Induction Docetaxel-Cisplatin Followed by Extended-field Radiotherapy in Patients with Cervical Metastases from Unknown Primary Carcinoma

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Abstract. Background: Cervical metastases from unknown primary tumors are rare and no clear therapeutic options are available. This retrospective analysis aimed to evaluate toxicity and activity of a sequential chemoradiation regimen consisting of induction chemotherapy followed by extended-field radiotherapy in patients with cervical metastases from unknown primary tumors. Patients and Methods: Patients with cytological or histological diagnosis of latero-cervical lymph-node metastasis from carcinoma with unknown origin treated with sequential chemotherapy (3 cycles of docetaxel and cisplatin, each administered as intravenous infusion at the dose of 75 mg/m2 on day 1, every 21 days) and radiotherapy (cumulative dose of 70 Gy) were included in this study. The radiological response was assessed by central review according to the revised RECIST criteria. Results: Fifteen patients received three cycles of induction chemotherapy with the combination of docetaxel and cisplatin. Patients were subsequently treated with extended-field radiotherapy. Three complete responses were observed after induction chemotherapy and 13 after the chemoradiation treatment. The overall response rate after chemoradiation was 93.3% (14 of 15 evaluable patients). One year disease-free-survival was 83.3% (10 of 12 evaluable patients). Treatment was well-tolerated; two cases of grade 4 neutropenia, two of grade 3 mucositis and eight of grade 2 nausea were the worst, most clinically-relevant side-effects. Conclusion: Induction chemotherapy followed by extended-field radiotherapy showed good activity and manageable toxicity in patients with cervical metastases from unknown primary tumors.

Carcinoma of occult primary tumor (COP) represents approximately 5% of all malignancies and 10-15% of all COP are diagnosed in the lymph-nodes of the neck (1). Cervical metastases from unknown primary tumors are often squamous cell carcinomas (65-75% of cases), while other histologies, such as undifferentiated (22%) and adenocarcinomas (13%), are less frequent (2-4). The primary tumor is frequently localized in the cervico-facial region and histology can guide the identification of the primary site. In fact, an undifferentiated carcinoma metastasized to cervical nodes is more likely to be derived from a nasopharyngeal tumor (4), whereas adenocarcinoma histology is associated with a salivary gland tumor. In case of a squamous histology, the lymph node level of involvement may be useful in the differential diagnosis of the primary site. The diagnostic work-up is complex, and includes computed tomography (CT), magnetic resonance imaging (MRI), panendoscopy with random biopsies and, most importantly, positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) (5, 6).

Although a multi-modality or single-modality approach including radiotherapy, surgery and chemotherapy is effective in patients with cervical metastases from COP, the optimal therapeutic strategy is yet to be defined in large phase III trials. One factor of the utmost importance is the degree of lymph node involvement. While single-modality radiotherapy-
or surgery-based treatment can be sufficient to treat N1 disease, a combined approach is required for N2 and N3 disease (7, 8). In the latter case, the disease is often systemic ab initio, as shown by the high rate of distant failure even after a radical surgery followed by radiation therapy (9). For such reasons we speculate that an approach including up-front chemotherapy followed by radiotherapy and surgery of residual disease could reduce the rate of systemic relapse in these patients. To provide preliminary, hypothesis-generating data regarding sequential use of chemotherapy followed by radiotherapy in patients with cervical metastases from COP, we conducted a retrospective review of all patients with COP treated at our Institutions. Only patients with cytotologically/ histologically-proved N2/N3M0 cervical COP undergoing sequential chemotherapy and radiotherapy were included in this analysis. Rigorous patient inclusion criteria were defined for this analysis and radiological scans were assessed by central reviewing according to a methodology that we discussed for kidney cancer (10).

Patients and Methods

Inclusion criteria. Patients meeting the following requirements were included in this retrospective analysis: (i) cytotological or histological diagnosis of latero-cervical lymph-node metastasis from carcinoma; (ii) failure to identify the primary tumor via a) physical examination with thorough evaluation of the head and neck mucosa using fiber-optic endoscopy, biopsies from all suspicious sites and blindly from the sites of possible origin of the primary; b) CT scan with and without contrast of the head, neck, thorax, abdomen and pelvis; c) PET/CT scan with FDG; (iii) N2 or more advanced lymphnode disease and no other sites of metastasis; (iv) treatment consisting of chemotherapy followed by radiotherapy; (v) radiographic images of CT scans and PET scans performed for staging and evaluation of response available for central review. This retrospective study was approved by the Institutional review board of the participating Institutions. All treatments were administered once written informed patient’s consent was obtained. A separate consent was obtained by all patients for clinical data use and publication in an anonymous way.

Retrieved data. Demographic data of eligible patients were retrieved along with clinical and histological characteristics such as Eastern Cooperative Oncology Group performance status, histological type and grading, and lymph node status. Data regarding chemotherapy and radiotherapy treatment were also extracted. Radiological images defining response rate and PFS were assessed by the central review using response evaluation criteria in solid tumors (RECIST) criteria version 1.1 (11). Toxic events were graded according to the National Cancer Institute common toxicity criteria (version 3.0), if applicable.

Data analysis. Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median numbers were presented with interquartile ranges. Overall response rate (oRR) to each line of treatment was defined as the percentage of patients who had either a complete response or a partial response or a stable disease as best response at any time during treatment. Survival and progression-free survival were computed from the start of chemotherapy to death or progression, respectively. The analysis was performed in November, 2012.

Results

Patients’ characteristics. From March 2010 to March 2012, a total of 15 patients with histological or cytotological confirmation of cervical metastases from unknown primary tumors were treated at our Department with induction chemotherapy followed by extended-field radiotherapy. Eleven patients were males, four were females. The median age was 50 (range=24 to 72 years). The patients’ characteristics are detailed in Table I.

Treatment. Initial work-up included CT of head, neck, chest and abdomen and whole-body PET/TC for all patients at baseline. An accurate evaluation of head and neck mucosa with a fiberoscopy followed by random biopsies from macroscopically normal areas completed the diagnostic step.

Induction chemotherapy consisted of three cycles of the combination of docetaxel and cisplatin, each administered as intravenous infusion at the dose of 75 mg/m² on day 1 which was repeated every 21 days. Three cycles were delivered to 13 patients, while the remaining two received two cycles of induction chemotherapy.

Radiotherapy consisted of a 3D conformational technique (3D CRT) for 11 patients and an intensity-modulated radiotherapy (IMRT) in two patients. All patients had previously undergone a comprehensive nutritional assessment and an accurate oral cavity examination with removal of necrotic teeth. Comprehensive irradiation was performed and both sides of the neck and all the mucosal areas, including nasopharynx, pharyngeal channel, larynx and oral cavity, were covered. When 3D CRT was performed, a total dose of 70 Gy was planned. For simultaneous integrating boost-IMRT, a total dose of 66.25 Gy to the planned target volume (PTV) was delivered. The treatment was performed using 6-MV photons with a linear accelerator administered in 2 Gy daily fraction for 3D CRT and 2.15 cGy for SIB-IMRT for five days weekly. For all patients, an electron beam boost (8-10 MeV) was given to the involved neck region up to cumulative dose of 70 Gy.

Assessment of toxicity and response. Blood cell counts, renal and liver function blood tests, as well as ECG, were performed weekly during chemotherapy. During radiotherapy, blood cell counts were checked on a weekly basis.

All patients were re-staged with a whole-body CT scan and a fiberoscopy examination at the end of the chemotherapy treatment. A re-staging CT scan and a fiberoscopy examination were carried out approximately 50
Efficacy. After induction chemotherapy, complete response (CR) was obtained in three out of 15 patients, while partial response (PR) was seen in 11 out of 15, and one patient had stable disease (SD). After the entire treatment, CR was observed in 13 out of 15 patients, PR in one patient and SD in another patient (the same one that did not respond to induction chemotherapy). The CR rate after induction chemotherapy and after radiotherapy was 20% and 86.6%, respectively. Complete response was also confirmed by PET scans for all of the 13 patients. The oRR after the entire treatment was 93.3%. At the time of this analysis, 13 patients were still alive and free of disease, while one patient had died due to an unrelated reason. Only one patient, who did not respond to chemotherapy nor to radiotherapy, died following tumor progression. The only patient who had PR after the entire chemoradiation plan underwent radical surgery and subsequently remained free of disease for about nine months; thereafter, he died of an unrelated traumatic event. Twelve out of 15 patients had a follow-up of at least 12 months and for these, a one-year DFS of 83.3% (10/12) was recorded. The remaining three patients had a follow-up shorter than one year but all of them had a CR and remained disease-free at the time of this analysis.

Toxicity. Fourteen out of 15 patients received all the three planned cycles of chemotherapy, while for one patient the docetaxel dose was skipped at the second cycle and reintroduced for the last cycle, due to a grade 2 hypertransaminasemia. Six out of 15 patients experienced grade 3 neutropenia and two suffered from Grade 4 neutropenia. Nevertheless, no patients required growth factor administration. Thirteen out of 15 patients completed the planned dose of radiotherapy (70 Gy); only two patients stopped treatment earlier (66 Gy) due to a Grade 3 mucositis. Grade 2 mucositis was the most frequent radiotherapy-related toxicity occurring in 10 out of 15 patients. All patients had a follow-up longer than 3 months and in 10 of them a grade 1 late xerostomia occurred. No treatment delays were observed due to toxicity. Toxicity is detailed in Table II.

Discussion

The best treatment for patients with cervical metastases from COP remains to be defined. Not only the optimal timing and use of surgery, chemotherapy and radiotherapy, but also the exact therapeutic approach, in terms of dosing and type of chemotherapy, surgical aggressiveness and field of irradiation remain to be defined.
Evidence that is presently available mostly derives from retrospective studies. Surgery followed by radiotherapy was the primary treatment in a cases series of 95 patients (12). Neck dissection was performed in 79 patients, while 16 patients underwent single lymph node sampling only. Postoperative radiation therapy was delivered to one side of the neck in 59 cases, and to both sides of the neck in the remaining 36 cases. Although limitations due to lack of study design and treatment protocol typical of retrospective studies do apply, it is interesting to note that bilateral neck irradiation did not appear to confer any advantage with respect to unilateral neck irradiation in terms of locoregional control and survival. Furthermore, at a median follow-up of 3.3 years, about one third of patients presented a local recurrence and a similar proportion presented a distant recurrence (12). In another retrospective experience, 60 patients with cervical metastases from unknown primary carcinoma, received either bilateral or unilateral neck irradiation or ‘extended field irradiation’, which included pharyngeal mucosa and bilateral neck nodes. Patients treated with ‘extended field’ radiotherapy did not appear to have a better prognosis, but the rate of primary site identification during follow-up was significantly lower in these patients, suggesting a possible benefit (13). A statistically significant survival advantage did emerge in favor of patients undergoing bilateral neck plus mucosal irradiation in a retrospective series of 82 patients with cervical node metastases from COP (14). Surgery was performed in 50 patients (60.9%). Out of 79 patients receiving radiotherapy, 37 patients (46.8%) received ipsilateral radiotherapy, while 42 patients (53.2%) received bilateral neck plus mucosal irradiation. Overall, the actuarial survival rates of the entire sample population 2, 5 and 10 years after diagnosis were 50.9%, 25.3% and 18.5%, respectively (14). Less recently, another retrospective study also suggested that bilateral neck irradiation is preferable with respect to ipsilateral irradiation. Of 52 patients with squamous cell COP to cervical lymph nodes, 36 were irradiated with a bilateral technique, while 16 were irradiated to the ipsilateral side of the neck alone. The occult primary was later discovered in 8% of the patients in the bilateral irradiation group and in 44% of the ipsilateral irradiation group ($p=0.0005$) (15).

More limited data are available as far as the role of chemotherapy is concerned. In a retrospective study involving 65 patients with cervical lymph node metastases of squamous cell COP treated with radiotherapy or chemoradiotherapy, 61 patients underwent surgical resection followed by postoperative radiotherapy with or without chemotherapy, four patients received definitive radiochemotherapy. After a median follow-up time of 64 months (range 3-219 months), the estimated 2- and 5-year overall survival rates were 71% and 48.7%, respectively. Unfortunately, the study data do not allow us to draw any conclusion regarding the benefit of adding chemotherapy to radiotherapy. Extracapsular spread, resection status, neck lymph node level, and Karnofsky index were significant prognostic factors for overall survival and recurrence-free survival at univariate analysis, with resection status and and level of involvement being significant predictors at multivariate analysis (16). These factors may therefore be helpful to identify patients requiring more aggressive treatments.

In our retrospective analysis, we present data on an original approach, consisting of inductive chemotherapy followed by extended, field radiotherapy. We selected patients with at least N2 disease, who are at worse prognosis, as discussed before. Our idea to use upfront chemotherapy was based on the high rate of distant relapse reported (12), while we felt that evidence was overall in favor of the use of extended-field radiotherapy. With minimal toxicity, we obtained CRs on CT scans, with confirmation on PET scans in 13 out of 15 patients, and 10 of 12 patients evaluable at one year after completion of treatment were free of disease. The several limitations of this study, which include the short follow-up period, its retrospective nature, as well as lack of a treatment protocol, demand caution while interpreting these results. On the other hand, it must be noted that the quality of the data presented here is significantly strengthened by the use of central radiographic review and by the selection of a homogenous study sample.

In conclusion, our preliminary experience shows that induction chemotherapy with cisplatin and docetaxel followed by radiotherapy may be associated with a high rate of complete radiological response in patients with cervical node metastases from unknown primary. Further investigation is warranted.

References


