PROMISING RESULTS WITH CHEMORADIATION IN PATIENTS WITH SINONASAL UNDIFFERENTIATED CARCINOMA

Danny Rischin, MBBS(Hons), FRACP, Sandro Porceddu, MBBS, FRANZCR, Lester Peters, MD, FRANZCR, Jarad Martin, MBBS, June Corry, MBBS, FRACP, FRANZCR, LeAnn Weih, PhD, MSc

Division of Haematology and Medical Oncology, Division of Radiation Oncology, and Statistical Centre, Peter MacCallum Cancer Centre, Melbourne, Australia. E-mail: Danny.Rischin@petermac.org

Accepted 5 November 2003
Published online 20 April 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.10396

Abstract: Background. Sinonasal undifferentiated carcinoma (SNUC) is an uncommon malignancy associated with poor prognosis. The optimal treatment approach for SNUC has not been established was performed.

Methods. A retrospective review of all patients with SNUC seen at the Peter MacCallum Cancer Centre over a 12-year period.

Results. Ten patients with SNUC were identified, with nine having locally advanced disease (T4). Seven were treated with three cycles of platinum and 5-fluorouracil followed by radiation with two cycles of concurrent platinum. In these seven patients, the 2-year progression-free survival was 43% (95% CI, 11% to 82%) and the 2-year overall survival was 64% (95% CI, 23% to 91%). One patient with a T1N0 nasal cavity tumor treated with radiation alone has not had a relapse. Two patients who were treated with initial surgical resection, prior to referral to our institution, received postoperative radiation, but they subsequently had relapses and died.

Conclusion. Induction chemotherapy followed by concurrent chemoradiation is a promising treatment strategy for SNUC.

Keywords: sinonasal undifferentiated carcinoma; induction chemotherapy; chemoradiation therapy

Sinonasal undifferentiated carcinoma (SNUC) is an uncommon malignancy first described by Frierson et al in 1986.1 It is a distinct clinicopathologic entity that must be distinguished from other sinonasal malignancies, including esthesioneuroblastomas, small cell carcinomas, nasopharyngeal-type carcinomas, and large cell lymphomas. An early report highlighted the aggressive nature of this tumor and the dismal prognosis.2 A subsequent report from the same group suggested that there might be a role for treating patients with preoperative chemotherapy and radiation, with a better outcome seen in some patients without extensive brain involvement.3 Many authors have subsequently advocated a multimodality approach incorporating surgery, radiotherapy, and chemotherapy.3,4 Locoregional control has been difficult to achieve in most series, with the clinical picture often dominated by the manifestations of locoregional failure, although patients with SNUC also have a propensity to develop distant metastases.

Based on the report by Deutsch et al5 reporting prolonged disease-free survival in a few patients treated with a combination of radiotherapy, CAV (cyclophosphamide, doxorubicin, and vincristine) chemotherapy, and surgery, the generally poor results with initial surgery and the fact that patients frequently present with unresectable...
disease, a policy evolved of treating patients with locoregionally advanced SNUC with induction chemotherapy, followed by concurrent chemoradiation, reserving any surgery for patients with residual disease. We elected to treat patients initially with a regimen similar to the one we were using for locally advanced nasopharyngeal carcinoma at the time with three cycles of induction chemotherapy consisting of cisplatin (or carboplatin) and infusional 5-fluorouracil (5-FU), followed by concurrent radiation with two cycles of platinum (cisplatin or carboplatin) in the first and last weeks of radiation.

**PATIENTS AND METHODS**

We conducted a retrospective review of all patients with paranasal sinus carcinoma treated at the Peter MacCallum Cancer Centre between April 1990 and April 2002. Our institutional ethics committee approved this study. We identified 10 patients who had presented to our hospital and been diagnosed with SNUC. Two of these patients had already undergone surgical resection prior to referral. Pathologists at our hospital reviewed the histology of all patients included in this series and confirmed the diagnoses (Figure 1). The diagnosis of SNUC was made primarily on morphologic grounds as has been described by Jeng et al.\(^5\) Patients who had morphologic features suggestive of nasopharyngeal-type undifferentiated carcinoma or esthesioneuroblastoma were excluded. Immunohistochemistry was used to aid in the exclusion of other differential diagnoses such as lymphoma, melanoma, and neuroendocrine tumors. Patients who had any definite areas of glandular or squamous differentiation within a predominantly undifferentiated tumor were also excluded. We reviewed the medical charts of all these patients to obtain data about their baseline characteristics and response to treatment. Patient characteristics are listed in Tables 1 and 2.

**Chemotherapy.** Induction chemotherapy consisted of three cycles of either cisplatin or carboplatin combined with infusional 5-FU. The cisplatin dose was 100 mg/m\(^2\) combined with 5-FU 1000 mg/m\(^2\) by continuous infusion for 5 days given at three weekly intervals. Carboplatin dose was calculated to target an area under the curve (AUC) of 5 and was combined with 5-FU 1000 mg/m\(^2\) by continuous infusion for 4 days given at three weekly intervals. Our policy in the early 1990s was to use cisplatin rather than carboplatin unless cisplatin was contraindicated. However, we subsequently adopted a policy of using carboplatin during the induction phase of chemotherapy to minimize the cumulative dose of cisplatin and risk of late toxicity including peripheral neuropathy and ototoxicity.

During radiation therapy, patients received two cycles of single-agent platinum generally in the first and last weeks of radiation. Throughout this time period, our policy was to use cisplatin during radiation therapy unless there was a contraindication, when carboplatin would be

![FIGURE 1. Histology from one of the SNUC cases demonstrating medium-sized cells with large ovoid nuclei, prominent nucleoli, and no evidence of squamous or glandular differentiation.](image-url)
Radiotherapy. All patients were treated with external beam megavoltage photon radiation therapy. Patients were immobilized supine in a customized cast. The majority of patients were treated using three fields, with a heavily weighted anterior field and two wedged laterals. CT planning was used for the last five patients, with the most recent patient planned using CT/MRI fusion. The median dose prescribed was 54 Gy (range, 50–60 Gy) in fractions of 1.8 to 2.0 Gy (except for one patient who received 50 Gy in 2.5-Gy fractions), delivered daily at five per week, to the isodose encompassing the planning target volume. The dose to the optic chiasm was limited to 54 Gy in all but one patient, who received 60 Gy because of gross tumor abutting the optic nerves and chiasm. Three patients with cervical nodal metastases received neck irradiation. Two patients received a total dose of 54 Gy, and the remaining patient, 50 Gy, in 2.5-Gy fractions, at five fractions per week. Treatment involved the use of parallel-opposed 6-MV photon fields. To keep the spinal cord dose 45 Gy or less, off-cord photon field reduction and bilateral posterior electron strips were used. The gross nodal disease was treated with at least a 2-cm field margin. Port films to verify isocenter and field placement were performed weekly. Patients were reviewed by a radiation oncologist on a weekly basis to assess radiation toxicity.

Statistical Methods. The close-out date for this study was 1 December 2002. The potential follow-up time for each patient was calculated as the time from treatment start to the close-out date. Overall survival and progression-free survival were estimated using the Kaplan-Meier (product-limit) method, with confidence intervals calculated using the logit transformation. For overall survival, all deaths were counted regardless of cause, and survival times for living patients were censored at the close-out date. For progression-free survival, the first progression at any site or death was counted as an event, and times were censored at the close-out date for patients who were alive at that date without progression. Time to progression for patients with persistent disease was counted from the first to last date of treatment. Only patients who were assessed in our multidisciplinary clinic prior to commencing treatment were included in the overall and progression-free survival analyses.

RESULTS
There were eight men and two women. The median age was 50 years (range, 36–84). At presentation, one patient had disease confined to the nasal cavity; the remaining nine patients had locally advanced disease, with three also having cervical node metastases. All patients had a baseline CT, nine had a MRI, and two had a positron emission tomography (PET) scan. Median potential follow-up was 43 months (range, 8–101 months).

Two patients were treated with initial surgical resection and were only assessed postoperatively in our multidisciplinary clinic. Both received postoperative radiation therapy. Both patients treated with initial surgery followed by radiation had a relapse, with locoregional and distant metastatic disease.
Of the eight patients who were seen in our head and neck multidisciplinary clinic prior to commencing treatment, seven were treated with induction chemotherapy followed by concurrent chemoradiation, with the only exception being an 84-year-old woman with a T1N0 nasal cavity tumor who was treated with radiation therapy alone. She has done very well, remaining disease-free for more than 5 years. However, the other patients presented with advanced disease (T4), similar to other series reported in the literature. Of the seven patients treated with induction chemotherapy followed by concurrent chemoradiation, two were treated with cisplatin and 5-FU and five received carboplatin and 5-FU induction chemotherapy. Six patients received all three planned cycles of induction chemotherapy, whereas one patient received only two cycles owing to progressive disease. Five patients received concurrent cisplatin during radiation and two received carboplatin. One patient who had received cisplatin during induction and week 1 of radiation received carboplatin in the final week of radiation because she had developed a peripheral neuropathy. All seven patients received two cycles of a platinum during radiation.

Four of seven patients achieved a partial response to induction chemotherapy, two patients had stable disease with symptomatic improvement including resolution of decreased sensation due to infraorbital nerve involvement, and one patient had progressive disease on chemotherapy. This patient also had a very short-lived response to radiation therapy and died 5 months after presentation. Four patients achieved a complete response following radiation, and they remain disease-free 8 to 51 months following presentation (Figure 2). None of the four patients who received 60 Gy have relapsed. Two patients had small areas of residual disease and have subsequently experienced relapses at these sites. Neither of these two patients had surgery for residual disease. Two-year progression-free survival was 43% (95% CI, 11% to 82%), and 2-year overall survival was 64% (95% CI, 23% to 91%) (Figure 3). No grade 3 or 4 late radiation toxicity has been observed.

**DISCUSSION**

There is no consensus about the optimal treatment of patients with SNUC. Owing to the rarity of this malignancy, there are no prospective trials, and the literature comprises small retrospective series and case reports. In the first reported series from the University of Virginia Health Sciences Center, only one of 11 patients remained alive at 10 months without evidence of disease.² Patients were treated with radiation, with seven also receiving chemotherapy. Subsequently, the same group reported on another six patients who were treated with CAV chemotherapy and radiation prior to surgical resection.³ At the time of the report, three patients were alive without recurrence at 18, 43, and 52 months. One of these patients had orbital involvement, and none had intracranial extension or nodal involvement. They concluded that the prognosis for patients with localized disease treated with this approach might be better than originally described. The experience from the...
University of Virginia has been updated in two recent reports by different authors. Musy et al. reported on 20 patients treated between 1986 and 2000 who were treated according to a policy of induction chemotherapy, usually CAV, followed by radiation (50–63 Gy) followed by craniofacial resection in patients who had resectable disease at the outset. Ten patients underwent craniofacial resection (CFR), three had a complete pathologic response, two had close margins, and two had positive margins or gross residual disease. Only three of the 20 patients remained alive without having experienced a recurrence at 36, 49, and 164 months. One of these three patients was staged as Kadish stage B, the other two as Kadish stage C, and all three had been treated with CAV chemotherapy, radiation, and CFR. Two had achieved a complete pathologic response to chemoradiation, and one had close margins following CFR. The third patient who had achieved a complete pathologic response developed distant metastases at 19 months. The second report describes 25 patients, which included eight patients from the previous reports. Specific details of treatment are not outlined in this article, but it is stated that patients invariably had radiation to the primary, many received extensive surgical resections, and variable chemotherapy regimens were administered, including treatment of two patients with high-dose chemotherapy and autologous bone marrow transplantation. Follow-up information was available for 16 patients. Of these 16 patients, at presentation only two were reported to have orbital involvement, two had intracranial extension, and none were reported to have had cervical node involvement. Despite the relatively limited extent of disease in most patients, 56% developed local recurrence, 50% cervical nodal recurrence, and 43% distant metastases. There was only one long-term disease-free survivor; all other patients had died of disease or remained alive with disease. It is of interest that the two patients who were treated with high-dose chemotherapy and bone marrow transplantation had extended survival, both dying from recurrent disease 9 years after initial presentation.

Gallo et al reported a 15.5% 5-year survival in a series of 13 patients with SNUC. Patients were treated predominantly by radiotherapy with or without chemotherapy. There were only two patients alive without disease, both having had localized disease. One had a T2N0 nasal cavity tumor treated by partial maxillectomy, and the other had a T3N0 nasal cavity tumor with ethmoid involvement treated by radiation. All patients with orbital involvement, nodal involvement, or intracranial extension died of disease. Miyamoto et al. reported on 14 patients with SNUC and staged them according to the criteria proposed by Kadish for esthesioneuroblastoma. Five patients were alive without recurrence, with survival ranging from 3 to 195 months. Only two of these five patients had Kadish stage C. Three had been treated with surgery and postoperative radiation, and two with radiation, and chemotherapy. Smith et al. reported on six patients treated with surgery and postoperative radiation, with only two remaining disease-free at 6 and 18 months. Jeng et al. reported on a series of 37 patients with SNUC. The median survival was 10 months, and only four remained alive disease-free. All four patients have been updated in two recent reports by different authors. Musy et al. reported on 20 patients treated between 1986 and 2000 who were treated according to a policy of induction chemotherapy, usually CAV, followed by radiation (50–63 Gy) followed by craniofacial resection in patients who had resectable disease at the outset. Ten patients underwent craniofacial resection (CFR), three had a complete pathologic response, two had close margins, and two had positive margins or gross residual disease. Only three of the 20 patients remained alive without having experienced a recurrence at 36, 49, and 164 months. One of these three patients was staged as Kadish stage B, the other two as Kadish stage C, and all three had been treated with CAV chemotherapy, radiation, and CFR. Two had achieved a complete pathologic response to chemoradiation, and one had close margins following CFR. The third patient who had achieved a complete pathologic response developed distant metastases at 19 months. The second report describes 25 patients, which included eight patients from the previous reports. Specific details of treatment are not outlined in this article, but it is stated that patients invariably had radiation to the primary, many received extensive surgical resections, and variable chemotherapy regimens were administered, including treatment of two patients with high-dose chemotherapy and autologous bone marrow transplantation. Follow-up information was available for 16 patients. Of these 16 patients, at presentation only two were reported to have orbital involvement, two had intracranial extension, and none were reported to have had cervical node involvement. Despite the relatively limited extent of disease in most patients, 56% developed local recurrence, 50% cervical nodal recurrence, and 43% distant metastases. There was only one long-term disease-free survivor; all other patients had died of disease or remained alive with disease. It is of interest that the two patients who were treated with high-dose chemotherapy and bone marrow transplantation had extended survival, both dying from recurrent disease 9 years after initial presentation.

Gallo et al. reported a 15.5% 5-year survival in a series of 13 patients with SNUC. Patients were treated predominantly by radiotherapy with or without chemotherapy. There were only two patients alive without disease, both having had localized disease. One had a T2N0 nasal cavity tumor treated by partial maxillectomy, and the other had a T3N0 nasal cavity tumor with ethmoid involvement treated by radiation. All patients with orbital involvement, nodal involvement, or intracranial extension died of disease. Miyamoto et al. reported on 14 patients with SNUC and staged them according to the criteria proposed by Kadish for esthesioneuroblastoma. Five patients were alive without recurrence, with survival ranging from 3 to 195 months. Only two of these five patients had Kadish stage C. Three had been treated with surgery and postoperative radiation, and two with radiation, and chemotherapy. Smith et al. reported on six patients treated with surgery and postoperative radiation, with only two remaining disease-free at 6 and 18 months. Jeng et al. reported on a series of 37 patients with SNUC. The median survival was 10 months, and only four remained alive disease-free. All four
Chemoradiation for Sinonasal Undifferentiated Carcinoma

Patients had localized disease and were treated by surgery, with three receiving postoperative radiation. All patients with nodal, orbital, or intracranial disease had died or were alive with disease. Review of the reported series of SNUC highlights the fact that in patients with orbital, nodal, or intracranial extension of disease, locoregional control and prolonged disease-free survival are rarely achieved.

In our series, the two patients treated with initial surgery followed by radiation have fared poorly, both having had a relapse. One patient with early-stage disease, a T1N0 nasal cavity tumor, has remained disease-free for more than 5 years following treatment with radiation alone. This is consistent with other reports of long-term survival in patients with early-stage disease treated with surgery or radiation. The seven patients treated with induction chemotherapy followed by chemoradiation had advanced disease, with all seven having T4 tumors, six having intracranial extension, six having orbital involvement, and three having involved cervical nodes. Despite these poor prognostic features, our results are very good with 2-year overall survival of 64% and four patients remaining alive without disease progression. It is noteworthy that of the seven patients with locally advanced disease treated with chemoradiation, all four patients who remain alive without relapse received 60 Gy radiation, whereas the three patients who had a relapse received 50 to 54 Gy. These results suggest that there may be a dose-response relationship in SNUC and that at least 60 Gy is required. None of our patients had surgery for residual disease, although in retrospect, patient 4, who had a small residual mass in the nasal cavity/nasopharynx following 50 Gy radiation, may have benefited from a higher dose of radiation and resection of residual disease. The other patient who had definite residual disease following chemoradiation (patient 7) had residual disease in the olfactory groove and involving the dura in the anterior cranial fossa but refused surgery.

Although SNUC is recognized to be a chemosensitive disease, data about responses to induction chemotherapy are limited. A group at The University of Texas M. D. Anderson Cancer Center have reported on their experience with undifferentiated ethmoid sinus carcinomas, in which six patients received chemotherapy with cisplatin, 5-FU, leucovorin, bleomycin, methotrexate, etoposide, or doxorubicin. All six patients achieved a complete or partial response to chemotherapy, although it is unclear whether patients included in this series had morphologic features of SNUC. Responses to CAV have not been reported, although it is stated that two of eight patients were switched to another chemotherapy regimen owing to lack of response. In our series, four of seven patients had objective responses to chemotherapy. The chemosensitivity of SNUC provides a sound rationale for the use of both induction and concurrent chemotherapy. The use of induction chemotherapy may improve both locoregional control and decrease distant metastases. It is noteworthy that no patient treated with induction followed by concurrent chemotherapy has to date developed distant metastases (follow-up 8 to 62 months), whereas both patients treated with surgery and postoperative radiation did develop distant metastases at 8 and 20 months, respectively. Induction chemotherapy may contribute to local control by reducing tumor bulk juxtaposed to vital dose-limiting critical structures such as the optic chiasm prior to radiation. Although planning target volumes should not be reduced on the basis of chemotherapy-induced response, the tumor bulk reduction following induction chemotherapy increases the probability that gross residual disease receives the full radiation dose. The lack of benefit with induction chemotherapy in squamous head and neck cancers is most likely due to accelerated repopulation of surviving tumor clonogens that offsets the cytotoxic effect of chemotherapy. However, because accelerated repopulation is a function of tumor differentiation, this is unlikely to limit the effectiveness of induction chemotherapy in an undifferentiated tumor such as SNUC. However, it must be acknowledged that the role of induction chemotherapy in other undifferentiated cancers, (eg, nasopharyngeal cancer) remains controversial. In undifferentiated nasopharyngeal carcinoma several studies have reported improved locoregional control with induction chemotherapy, although none of these studies has shown improved overall survival. Administration of platinum-base chemotherapy concurrent with radiation has been demonstrated to improve locoregional control and survival in a number of malignancies, hence it is reasonable to speculate that it may do so in SNUC, particularly because the radiation dose that can be delivered in SNUC may be constrained by the proximity of the tumor to vital dose-limiting structures. Furthermore, platinum drugs can be combined with radiation without markedly increasing normal tissue toxicity. In contrast,
anthracycline-containing regimens, such as the CAV regimen that has been used for SNUC, are difficult to administer concurrently with radiation. Our series is the first to report the use of chemotherapy concurrent with radiation therapy.

With the emergence of improved diagnostic imaging tools, such as helical CT, MRI, PET, and innovative radiotherapy technology, such as CT planning and three-dimensional conformal and intensity-modulated radiotherapy, dose escalation to the planning target volume without increased complications to critical structures may be possible. The potential risk of geographical miss is also reduced. These advances in technology may theoretically improve outcome.

In conclusion, the regimen of three cycles of induction platinum and 5-FU chemotherapy followed by concurrent radiation and platinum chemotherapy is feasible, associated with excellent compliance, has acceptable toxicity, and is a promising treatment approach for patients with locoregionally advanced SNUC. Taking into account the generally poor results in the literature, our promising results in a group of patients with adverse prognostic features and the fact that SNUC is a rare disease in which it is not possible to conduct randomized trials, our current policy is to treat these patients with chemoradiation, reserving surgery for patients who have definite residual disease that is resectable following chemoradiation.

Acknowledgments. We thank Hugh Turner and Bill Murray in the Department of Pathology at the Peter MacCallum Cancer Centre for reviewing the pathology of patients included in this report.

REFERENCES