Clinical management of localized undifferentiated sinonasal carcinoma: our experience and review of the literature

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Undifferentiated sinonasal carcinoma (SNUC) is defined as a small round blue cell tumor that is immunohistochemically distinct from other sinonasal malignancies, such as lymphoma, mucosal melanoma, nasopharyngeal carcinoma, neuroendocrine carcinoma, and olfactory neuroblastoma. SNUCs are very aggressive malignancies, provoking quick destruction of the splanchnocranium structures. Being a very rare neoplasm, there are no prospective clinical trials assessing their treatment strategies, so lots of data are derived by small retrospective trials. Tri-modality treatments (namely those treatments which use together surgery, radiation therapy and chemotherapy) are now considered the best of care for this category of poor prognosis tumors, and whenever possible they should be employed. Despite the tri-modality treatments and the multidisciplinary management, SNUCs are characterized by poor prognosis with a median overall survival reaching 14 months. Ameliorating radiotherapy techniques and performing therapies adapted to the genetics of the disease could represent a promising strategy of therapy in the near future. In this report, we have presented our experience, describing the treatment and the prognosis of four patients seen at our Institution. Moreover, we have performed a review of the literature analyzing the now available therapy options and the possible future strategies. ***Anti-Cancer Drugs*** **30:308–312**

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Background

A wide range of malignancies with distinct histology can occur in the sinonasal tract, as they can be composed of cancer cells with no definitive differentiation, round cell morphology with high nuclear-to-cytoplasmic ratio, high mitotic and apoptotic activity, and necrosis. Differential diagnosis of these tumors is often challenging and includes a wide number of epithelial and nonepithelial malignancies [1].

Poorly differentiated sinonasal malignancies should be strictly distinguished from other cancer types, as they show distinctive clinical behavior and, most importantly, different response to therapy. Undifferentiated sinonasal carcinoma (SNUC) is defined as a small round blue cell tumor that is immunohistochemically distinct from other sinonasal malignancies, such as lymphoma, mucosal melanoma, nasopharyngeal carcinoma, neuroendocrine carcinoma, and olfactory neuroblastoma. SNUC is a rare and clinically aggressive neoplasm, originating from paranasal sinuses or, rarely, from nasal cavity, and rapidly invading the adjacent sinonasal structures, the orbit, the skull base, and the brain [2].

From the histological standpoint, SNUC is positive for epithelial markers, such as cytokeratins and epithelial membrane antigen. Moreover, it shows variable expression of neuron-specific enolase, chromogranin, and synaptophysin, and it can show partial positivity for p63 and p40. On the contrary, SNUC is typically negative for Epstein–Barr virus, and its association with HPV infection has been reported with low frequency [3].

Recently, some author have discovered a high frequency of isocitrate dehydrogenase (IDH2) mutations in SNUC. Isocitrate dehydrogenase is a digestive enzyme that is used in the citric acid cycle. Its main function is to catalyze the oxidative decarboxylation of isocitrate into α-ketoglutarate. This kind of mutation is also present in a number of solid tumors, such as glioma, cholangiocarcinoma and chondrosarcoma and hematologic malignancies. The mechanisms through which IDH2 deregulation causes cancer are unknown [4,5].

SNUCs often are diagnosed at the fifth–sixth decade of life with a male/female ratio of 3 : 1. The main known risk factor is the exposure to wood dust, even if the tumorigenesis of SNUC is still widely unknown [6].

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As reported above, SNUC is characterized by poor prognosis if compared with other sinonasal malignancies as they often relapse, both locally and at distance sites, after upfront therapy [7,8].

Considering the very low incidence of SNUC, there is a lack of prospective randomized clinical trials aimed at defining standard therapies, thus treatment guidelines are mainly based on the results of retrospective studies and meta-analysis of data collected from single institution experiences.

Standard treatment strategies

SNUC presents as a rapidly enlarging mass involving many areas of the sinonasal cavity with common invasion of adjacent structures. Importantly, SNUC has the capability not only to exert aggressive local destruction but also to determine regional spread and distant metastases. Patients often present with nonspecific symptoms, such as epistaxis and nasal obstruction. This leads to a delay in diagnosis, which is often reached in the advanced stage of disease [8–10].

Surgery represents the mainstay of treatment for all the sinonasal malignancies, including SNUC. Nevertheless, radical surgical excision is not frequently achieved, whereas R1 or R2 procedures (microscopically or macroscopically involved resection margins, respectively) are very common, especially in case of SNUC, owing to their local invasiveness. Common surgical interventions consist in maxillectomy together with resection of ethmoid sinuses and nasal cavities, followed by reconstruction of the splanchnocranium. Importantly, the intent of surgery should always be to achieve a radical excision, as R0 resections correlate with significantly longer survival in comparison with R1/2 resections [8,10,11]. Radiation therapy should follow surgery. International guidelines, such as the National Comprehensive Cancer Network guidelines, strongly recommend adjuvant radiotherapy also in presence of R0 resection, especially for locally advanced disease (T3/T4) [11–13]. Concurrent adjuvant chemoradiotherapy was shown to be superior to adjuvant radiotherapy alone in several clinical reports. The utility of treatment strategies comprising systemic chemotherapy associated with local radiation therapy may be explained by the early propensity of SNUC to spread to distant sites. In general, data from literature strongly suggest that tri-modality treatments lead to a better survival compared with bimodality and/or mono-modality strategies. In fact, patient prognosis appeared to be significantly better when upfront surgery was followed by chemoradiation in comparison with surgery alone (mono-modality treatment) and/or surgery followed by radiotherapy alone (bimodality treatment) [14–18]. Moreover, induction chemotherapy or neoadjuvant chemoradiotherapy followed by surgical excision did not appear superior to upfront surgery followed by adjuvant chemoradiation [19–23]. Several chemotherapy agents have been employed concurrently with radiation therapy, but the most widely used is cisplatin.

The molecular mechanisms leading to tumor initiation and progression are still largely unknown for SNUC, and currently no 'driver mutations' have been identified. Therefore, no targeted therapy has been tested so far in SNUC [24], and traditional chemotherapy still represents the only systemic treatment available for SNUC treatment.

In summary, considering the available evidence from the literature focusing on the treatment of SNUC, it is well defined that these malignancies should be treated with radical surgery (R0), whenever possible, followed by adjuvant chemoradiation (concurrent cisplatin-radiotherapy). However, despite applying the best tri-modality treatment strategy, survival rates at 5 years do not exceed 30%, and reported median overall survival (OS) is about 14 months; thus, SNUC is still considered a disease with poor prognosis.

Our experience

From March 2005 to March 2017, four patients with diagnosis of SNUC have been treated at our Institution (IRCCS G. Pascale, Naples, Italy). Since the diagnosis, all the patients were followed by a multidisciplinary team comprising clinical oncologists, radiation oncologists, a pathologist, a radiologist and a surgeon.

Diagnosis and staging

Pathologic diagnosis was initially obtained by direct biopsy of the lesion. Pathologic diagnosis of SNUC was assessed at first histopathologic examination, after the diagnostic biopsy, and it was confirmed after surgical intervention, which was performed in all the patients. Two out of four primitive tumors arose from nasal cavity, one from sphenoidal and one from maxillary sinus. Disease was staged with computed tomography (CT) scan of the head, neck, thorax and abdomen. None of the screened patients had a metastatic disease.

Treatment

All the patients were treated with upfront surgery followed by adjuvant chemoradiation (tri-modality therapy). As per standard procedure, surgery aimed to achieve complete resection of the tumor with negative margins. The type and the extension of surgical procedure was dictated by the onset site and the disease extent. The employed surgical techniques included total maxillectomy, and/or ethmoidectomy, and craniofacial resection. Elective lymph node resection was not performed because no clinically positive lymph node metastases were detected in the four patients. In all the cases, surgery was confirmed to be radical, obtaining a R0 resection.

Adjuvant chemoradiotherapy was delivered to all the four patients after a time ranging from 30 to 60 days. All

patients were treated with three-dimensional (3D)-conformal radiotherapy. Treatment planning was based on CT scan examination performed with the patients in supine position using head–neck–shoulder thermoplastic devices. The target and organs at risk (OARs) were defined on a CT planning scan. Clinical target volume included the resection cavity plus all paranasal sinuses that had been invaded or were at high risk of invasion. Elective nodal irradiation was not performed. Planning target volume was defined as clinical target volume plus a 5-mm isotropic margin. OARs included the retina, optic nerve, and optic chiasm. A median total dose of 60 Gy (range: 50–64 Gy) was delivered in 30 daily fractions of 2 Gy. The maximum dose of 54 Gy was used as dose constraint for OARs for planning elaboration. The fields were arranged and weighted to achieve the maximum possible uniform distribution in the target volume (95% of prescription dose delivered to $\geq$ 95% of the planning target volume) without exceeding the dose constraints for the OARs. Concomitant cisplatin was administered at a dose of 100 mg/m^2 for three cycles during radiotherapy, on days 1, 22, and 43.

Patient outcomes

One patient, a 58-years old male, with diagnosis of nasal cavity SNUC is still alive, and his OS is currently 148 months. The staging at diagnosis was T3N0M0. The patient received 60 Gy of adjuvant radiotherapy combined with three planned cycles of cisplatin and experienced grade 2 mucositis during the treatment.

The second patient, a 62-years old male, with diagnosis of nasal cavity SNUC experienced an early tumor recurrence. He presented latero-cervical lymph node relapse and died 5 months later (OS: 10 months). The staging at diagnosis was T4N0M0, and the total dose of adjuvant radiotherapy delivered was lowered to 50 Gy, owing to acute early toxicity, consisting of grade 3 mucositis. In this patient, only two out of three planned cycles of cisplatin could be administered.

A third patient with SNUC arising from sphenoid sinus was a 59-years-old male. He experienced local disease relapse, arising from hard palate, after 72 months from primary diagnosis. He died after 8 months from recurrence. The stage at diagnosis was T4N0M0 and the total dose of adjuvant radiotherapy reached was 64 Gy. No severe acute toxicity was encountered, being grade 1 mucositis the only observed adverse effect.

Finally, the fourth patient was a 68-years old male with diagnosis of maxillary sinus SNUC. He is still alive, and his OS is 27 months, so far. The staging at diagnosis was T3N0M0, and a total dose of 58 Gy was delivered as adjuvant radiotherapy. Acute grade 2 mucositis was recorded after about 34–36 Gy.

Summarizing, none of the four patients had very advanced SNUC at diagnosis, as they were all N0 and M0. Surgery was radical in all the four cases and the planned dose of adjuvant radiotherapy was almost reached in all of the cases. The only patient experiencing poor prognosis was not able to tolerate adjuvant chemoradiation. No late toxicities have been recorded, and in particular, no radiotherapy-relate blindness has been observed.

Discussion

SNUCs are very rare neoplasms arising from nasal cavity and paranasal sinuses, which show the poorest prognosis among other sinonasal malignancies (squamous cell, adenocarcinoma, adenoido-cystic and muco-epidermoid), as median OS described in literature does not exceed 14 months [7].

The only data available regarding survival and objective response rates are provided by retrospective studies and single case reports, owing to obvious difficulties in accomplishing prospective trials in such rare diseases. Some authors have tried to perform meta-analyses based on published retrospective studies, but also in this case, several biases have been encountered, considered the retrospective nature of the originating data.

Despite the lack of level I evidence, based on the available data, we can define some firm points for the clinical management of SNUC.

First, these should be treated with multimodality treatments, in particular tri-modality treatment. Integration of surgery with chemotherapy and radiation therapy should represent the standard of treatment. Several data are in favor of upfront surgery followed by concurrent chemoradiation, whereas the role of induction chemotherapy or chemoradiotherapy remains still unclear.

Another important aspect regards the need of negative margins after surgical excision, as R1 and R2 interventions are associated with higher recurrence rate.

Third point to consider is the technique of radiotherapy employed. We have used conformal 3D radiation therapy achieving fairly good results, in terms of both survival and toxicity. Nevertheless, it is well acknowledged the possibility to obtain better outcome and significantly lower toxicity by employing intensity modulated radiation therapy (IMRT) and volumetric multiparametric arc therapy (VMAT), in comparison traditional two-dimensional and 3D techniques. Gamez *et al.* [25], for example, demonstrated better OS associated with the use of IMRT/VMAT versus conformal 3D radiotherapy. The authors also highlighted that doses higher than 60 Gy were associated with improved survival [26]. Toxicity spectrum is also improved by IMRT/VMAT. As matter of fact, data provided by retrospective studies showed a lower rate of radiotherapy-related blindness when IMRT rather than conformal 3D radiation therapy was used.

Finally, it is important to define the role of concurrent chemotherapy associated with radiation therapy. Data from the literature strongly encourage the use of chemoradiation in site of radiotherapy alone, owing to the better outcome observed with the concomitant treatment.

In our report, we have employed the tri-modality treatment that integrates upfront radical surgery with chemoradiation, achieving good patient outcomes. Specifically, two of four patients are still alive and a third patient had a particularly long OS (80 months). Only one patient experienced an early recurrence after receiving a suboptimal adjuvant treatment owing to poor tolerance to radiation therapy. Although the sample size of our report is too small to perform statistical analyses, we believe that our experience can be of interest, given the excellent outcome and the favorable toxicity profile observed, even if a conformal 3D technique was employed.

Conclusion and future perspectives

SNUCs are particularly difficult to treat owing to their clinical and biological aggressiveness and to the lack of prospective trials. In addition, these malignancies appear to be quite radioresistance and chemoresistant, and this feature may be because of their hypoxic status, which is, notoriously, a factor associated with scarce response to ionizing radiations. In addition, radioresistance and chemoresistance of SNUC may by caused also by their molecular heterogeneity, which is associated with high numbers of neoplastic clones, with the capability of developing resistance to ionizing radiations and/or chemotherapeutic drugs.

The use of tri-modality therapies can improve patient outcome and the employment of IMRT/VMAT can also ameliorate the safety profile of treatment. Nevertheless, the prognosis of SNUC remains very poor, and novel therapeutic strategies are strongly needed.

A promising new treatment approach may be based on the use of carbon ion radiotherapy (CIRT). Indeed, CIRT has superior dose distribution, higher linear energy transfer, and higher relative biological effectiveness, in comparison with conventional photon-based radiation therapy. These capabilities are probably owing to the unique DNA damage signature, which is characterized by clustered lesions which overload the DNA repair capacity of malignant cells. CIRT may be an excellent new weapon against SNUC, but its role as adjuvant radiotherapy is still unknown as its efficacy was primarily shown so far in the presence of un-resected tumors [27].

Another promising treatment strategy could be the morpho-proteomic-guided treatment, namely, the pretherapy assessment of SNUC. This approach is based on DNA analysis of tumor tissue followed by personalized therapy. Ansari *et al.* [28] treated two patients affected by SNUC with a combination of induction therapy, performed on the basis of genetic signature of the tumor, followed by chemoradiation, and obtained two complete response and long survival of both the patients. In the morpho-proteomic analyses, the authors analyzed the mTOR pathway, the topoisomerase II and the fatty acid sintase status. Based on the results of these analyses, they used a chemotherapy scheme containing adriamycin, metformin, and etoposide followed by concurrent cisplatin-radiotherapy.

A further step forward could be identifying specific gene signatures of SNUC using tissue samples collected by biopsy, and subsequently adapting systemic therapy to the molecular portrait of disease. IDH2 mutations are often found in SNUC, and at present, drugs inhibiting IDH2 enzyme have yet reached the clinic, being commonly used in hematologic malignancies. Their future employment may be taken into account in SNUC.

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Conflicts of interest

There are no conflicts of interest.

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