Chapter 9
The Role of Systemic Therapy and Targeted Approaches for the Treatment of Sinonasal Malignancies

Paolo Bossi, Luigi Lorini, Francesca Consoli, and Salvatore Grisanti

Neoadjuvant or Induction Therapy

The advantages of such an approach mainly concern the possibility to reach an adequate level of dose intensity with a potential improvement in anti-tumor activity. Generally, patients better tolerate a neoadjuvant cytotoxic therapy compared with adjuvant therapy, and the response to this strategy could select more radio-sensitive diseases. However, one may argue that such an approach can lead to a delay in curative treatment, either surgical or radiotherapy (RT), which remains the only procedures with a proven possible curative potential.

There are several retrospective studies or monocentric reports that have shown the possible advantages of chemotherapy administered before curative approaches [1].

Lorusso et al. reported the outcome of 16 patients with sinonasal cancer (SNC), mostly squamous cell cancer, treated with platinum-based induction chemotherapy followed by RT. The overall response rate, pathological complete response (pCR), and partial response (PR) rates were of 82%, 44%, and 38%, respectively. These data were the first to show the activity of systemic induction treatment [2].

Subsequent papers published in 1992 and 1999 confirmed the efficacy of systemic induction treatment. In 1992, a pilot study evaluated the possibility of tumor control and organ preservation in 12 patients with advanced non-adenocarcinoma of the paranasal sinus and nasal fossa after induction treatment with cisplatin +5-fluorouracil (5-FU; PF). The curative treatment was external radiotherapy with 48 Gy and surgery. Eight patients showed no signs of pathological disease. A total of 11 patients had disease control at the 27-month follow-up, and 10 of them were alive. This study was the first to explore the role of induction chemotherapy for organ preservation in SNCs [3].

P. Bossi (✉) · L. Lorini · F. Consoli · S. Grisanti
Medical Oncology Unit, Department of Medical & Surgical Specialties, Radiological Sciences & Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy
e-mail: paolo.bossi@unibs.it

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A study published in 1999 reported the monocentric experience of 29 stage III and IV SNC patients treated with multimodal treatment. Of these, 16 received three cycles of PF chemotherapy followed by concomitant chemoradiotherapy (with hydroxyurea and 5-FU). The study showed interesting clinical response data (87% of patients), a complete histological response (31%), 10-year overall survival (OS; 54%), disease-free survival (DFS; 67%), and local control (76%).

These data could be indirectly compared with recent findings in patients with the same disease setting treated with surgery followed by RT and showing 10-year OS of approximately 40% [4]. In 2003, Licitra et al. published an Italian series of 49 patients with resectable paranasal sinus tumors treated with chemotherapy (PF + leucovorin [PFL]) followed by surgical treatment and adjuvant RT. The study confirmed the relatively favorable OS shown in the previously reported experiences (3-year OS 69%). Moreover, it confirmed the positive prognostic role of the response to induction therapy and it stressed the importance of an adequate control of toxicities during this neoadjuvant approach, to avoid thromboembolic and cardiological complications [5]. Another retrospective study reported the treatment of 46 patients with treatment naïve sinonasal squamous cell carcinoma (SCC). Patients were treated with induction chemotherapy, with a regimen consisting of platinum and taxanes and nine patients were subjected to taxanes +5-FU. The data confirmed a relatively good 2-year OS (67%), in patients with unfavorable initial characteristics (80% stage IV; 67% orbital invasion; 26% nodal metastases). Moreover, it confirmed the role of induction therapy in organ preservation, as 87% of the patients avoided orbital exenteration. The response to induction treatment was a positive prognostic factor, regardless of the locoregional treatment [6]. It remains difficult to draw tangible conclusions as far as any significant improvement in the rate of structure preservation based on these retrospective single institution series. Although these studies show the importance of systemic treatment as part of a multimodal and multidisciplinary treatment both in improving survival and promoting organ preservation, they have several limitations. First, they are all retrospective or monocentric, non-randomized studies. In fact, until now, phase III randomized trials of induction therapy in the setting of head and neck cancers generally excluded patients with SNC. Second, no stratification by histotypes has been performed, which could be useful to tailor the therapeutic pathway.

Ongoing or recently concluded trials of induction chemotherapy will shed light on this topic. The Italian trials “Sintart 1” and “Sintart 2” with histology-driven chemotherapy followed by surgery or RT (photon and heavy ion therapy) have reached their accrual and results are now pending (NCT02099175; NCT02099188). In addition, the ECOG-ACRIN Cancer Research Group is carrying out a phase II randomized trial of neoadjuvant chemotherapy followed by surgery and RT versus surgery and postoperative RT in squamous cell sinonasal carcinoma (NCT03493425) with a combined endpoint of organ preservation, as well as OS. The MD Anderson Cancer Center is leading a trial of induction docetaxel, cisplatin, and 5-FU chemotherapy in locally advanced squamous cell or poorly differentiated SNC (NCT00707473). A crucial point in this regard will be the identification of patients who are responsive to neoadjuvant chemotherapy before the start of treatment.

Translational studies in other histologic types showed that gene expression may help identify patients who respond to chemotherapy, thereby maximizing the therapeutic effect in this patient population and sparing other patients from unnecessary toxicities [7]. Different and specific gene-expression profiles may be exploited for elucidating SNC biology and could help to identify prognostic and therapeutic opportunities [8].

In addition, radiomics could help in distinguishing patients who are responsive to systemic treatments administered before locoregional curative approaches. In a recent work, Bologna et al. [9] built and tested several radiomic-based predictive models of response to induction chemotherapy in SNC and suggested the relevance of apparent diffusion coefficient (ADC)-based radiomics in this regard.

Main series present in literature of induction chemotherapy are resumed in Table 9.1.

Adjuvant Systemic Therapies

A recent paper reporting data of the US National Cancer Database revealed that for SCC, patients who received adjuvant RT (hazard ratio [HR]: 0.658; $p < 0.001$), adjuvant chemoradiotherapy (HR: 0.696; $p = 0.002$), or neoadjuvant therapy (HR: 0.656; $p = 0.007$) had improved OS compared to surgery alone [18].

There are no data comparing postoperative RT with postoperative concurrent chemoradiation in SNC. Trials aimed at evaluating the added value of systemic therapy as radiosensitizers in operated head and neck cancers did not consider SNC, making it difficult to extrapolate results. However, the addition of chemotherapy to RT should be evaluated according to some clinical parameters: the pathological risk factors, the foreseen toxicity of the whole treatment package, the patient performance status and functionality, the risk of locoregional recurrence, and the risk of inducing distant metastases. Considering all these parameters, a rational choice may be made on a case-by-case basis. Only scarce and inconclusive data are available for adjuvant chemotherapy alone and this approach cannot be recommended [19].

Targeted Therapies and Immunotherapy

Targeted treatments obviously require a druggable target. Therefore, when considering a molecular target in SNC, we should understand whether the identified alteration is clinically actionable and if it has a druggable/predictive/prognostic value, or if it has diagnostic implications. In this regard, several molecular alterations have been described in SNC, mainly in terms of overexpression and mutations. Among the most frequently reported alterations in SNC, there are *EGFR* and *HER2* overexpression and mutations, *TP53* mutation, *cKIT* mutation, as well as overexpression of VEGFR, NF-κB, FGFR1, and COX2 [1].

Table 9.1 Induction chemotherapy in sinonasal cancers: single institutions studies

Author, years	Histology	Stage	Patients (*n*)	Chemotherapy regimen	OS (%)	DFS (%)	ORR (%)
Lorusso et al., 1988 [2]	SCC, SNUC, adenocarcinoma, SmCC	III, IV	16	5FU + cisplatin + methotrexate; doxorubicin; bleomycin	–	–	82
Bjork-Eriksson et al., 1992 [3]	SCC, PNET, anaplastic	I, III, IV	12	Cisplatin + 5FU	91 (2 years)	83 (2 years)	70
Lee et al., 1999 [4]	SCC, SNUC, mucoepidermoid	III, IV	19	Cisplatin + 5FU	73 (5 years)	67 (5 years)	87
Musy et al., 2002 [10]	SNUC	B, C[a]	15	CAV; cisplatin + 5FU; cisplatin + etoposide	64 (2 years)	–	–
Licitra et al., 2003 [5]	SCC, adenocarcinoma	I–IV	49	PFL	69 (3 years)	–	43
Licitra et al, 2004 [11]	ITAC	II–IV	30	PFL	–	66 (4,5 years)	40
Rischin et al., 2004 [12]	SNUC	IV	10	Cisplatin + 5FU	64 (2 years)	43 (2 years)	57
Rosenthal et al., 2004 [13]	ENB, SNUC, SNEC, SmCC	I–IV	72	Cisplatin + 5FU; docetaxel; etoposide	72 (5 years)	68 (2 years)	–
Kim et al., 2004 [14]	ENB	B, C[a]	11	VIP	–	–	82
Loy et al., 2006 [15]	ENB	A, B, C[a]	50	Vincristine + cyclophosphamide	–	86 (5 years)	–
Hanna et al., 2011 [6]	SCC	III, IV	46	Cisplatin + taxanes + ifosfamide or 5FU	67 (2 years)	–	67
Hirakawa et al., 2016 [16]	SCC	II–IV	43	Cisplatin + 5FU	71	67 (5 years)	93
Amit et al., 2016 [17]	SNUC	II–IV	95	Cisplatin + etoposide or docetaxel	56 (5 years)	53 (2 years)	67

Legend: OS overall survival, *DFS* disease free survival, *ORR* overall response rate, *SCC* squamous cell carcinoma, *SNUC* sinonasal undifferentiated carcinoma, *SmCC* small cell carcinoma, *PNET* primitive neuroectodermal tumor, *ENB* esthesioneuroblastoma, *ITAC* intestinal-type adenocarcinoma, *5-FU* 5-fluorouracil, *CAV* cyclophosphamide + doxorubicin + vincristine, *PFL* cisplatin + 5-fluorouracil and leucovorin, *VIP* etoposide + ifosfamide + cisplatin

[a]According to Kadish system

Dealing with potentially druggable alterations, a high frequency of targetable *EGFR* mutations has been identified in SNC arising from inverted papillomas, with a possible role of EGFR inhibition [20].

A case report of SNC with *cKIT* exon 11 mutation achieving a durable response to imatinib has been recently reported; at the appearance of secondary *KIT* exon 17 mutation, the patient was additionally treated with regorafenib [21].

As far as immunotherapy is concerned, preclinical data showed that PD-L1 expression is reported in 34% and 45% of tumor and immune infiltrates of SCC, respectively, while the corresponding frequencies in intestinal-type adenocarcinoma are 17% and 33%, respectively [22]. In another paper, 30% of the patients with squamous cell SNC showed PD-L1 expression in >5% of tumor cells and PD-L1 expression significantly correlated with poor differentiation and a high level of tumor-infiltrating lymphocytes [23].

As of now there are no trials specifically addressing immunotherapy in SNCs.

Systemic Therapy in Different Histotypes

Intestinal-Type Adenocarcinoma

An Italian study confirmed the prognostic role of favorable response to induction chemotherapy with PFL regimen (platinum, 5-fluorouracil, and lederfolin) in this histology. Pathologic complete response (pCR) was obtained after induction chemotherapy with PFL in 40% of the treated cases. An interesting finding was that the presence of functional p53 positively correlated with pCR. Moreover, tumors bearing a functional p53 had an improved survival only when the treatment comprised induction chemotherapy plus surgery and RT, while the same prognostic factor was not confirmed in patients treated only with surgery and RT [11, 24].

Neoadjuvant chemotherapy may, therefore, be considered in intestinal-type adenocarcinoma patients with a functional p53 who are fit to receive this treatment.

Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinomas (SNUCs) are among the most aggressive histotypes in SNC, as they have a high rate of locoregional recurrence and high tendency to metastasize. Several retrospective series have shown the effectiveness of chemotherapy regimens within a multimodal approach, in reducing the risk of locoregional and distant recurrence, when compared to patients not having received systemic treatments. However, defining a standard chemotherapy regimen is complicated given the variety of approaches employed [25].

A study conducted in the United States showed a 2-year OS for 64% for patients with locoregional disease undergoing induction chemotherapy (mainly the cyclophosphamide doxorubicin, vincristine [CAV] regimen) followed by radiation and surgery. Survival dropped to 25% for patients not amenable to surgery [10].

Another trial showed the efficacy of the PF scheme followed by concomitant RT with a 2-year progression-free survival of 43% and a 2-year OS of 64%. The incidence of distant metastases in this trial decreased in patients treated with induction chemotherapy and subsequent concurrent chemoradiotherapy compared to patients treated with surgery and postoperative RT [12].

These data are confirmed by a study showing 63% of patients displaying a 5-year OS and a distant metastases rate of 25% in patients with locally advanced SNUC undergoing induction chemotherapy followed by RT whether or not combined with chemotherapy [13].

Recently, in a large series of SNUC, in patients who achieved a favorable response to induction chemotherapy, definitive chemoradiation improved survival in comparison to surgery followed by RT; on the other hand, in patients without response to induction therapy, bearing a worse prognosis, the addition of surgery could provide a better chance of disease control over chemoradiation alone. Response to induction therapy could, therefore, be a guide for subsequent curative approach [17].

Sinonasal Neuroendocrine Carcinoma

The largest retrospective series in the literature has no more than 20 patients with sinonasal neuroendocrine carcinoma. In these analyses, the approach for locally advanced disease is often multimodal and involves neoadjuvant chemotherapy of platinum with 5-FU, docetaxel or etoposide. Therefore, despite the limitations of small numbers, multimodality treatments comprising induction chemotherapy are a choice also in sinonasal neuroendocrine carcinoma [13].

An analysis of an Italian multicenter database revealed that induction chemotherapy is associated with improvement in OS (HR: 16.8; $p = 0.01$) and DFS (HR: 4; progression-free survival: 0.04) independent of other clinicopathological characteristics, confirming the relevance of induction chemotherapy in a multimodal approach [26].

Olfactory Neuroblastoma (Esthesioneuroblastoma)

Olfactory neuroblastomas are neuroectodermal tumors with relatively good prognosis in locally advanced cases, when treated with surgery followed by RT. A few studies have analyzed the possible role of chemotherapy in a predominantly

neoadjuvant setting, but the data are not robust enough to represent a strong recommendation [1].

One study showed long-term disease control results (15-year DFS: 83%) with chemotherapy (vincristine + cyclophosphamide) followed by RT and surgery [15].

A series of 11 patients showed a response rate of 82% for patients undergoing chemotherapy in neoadjuvant setting with the VIP regimen (etoposide + ifosfamide + platinum) [14].

Data would suggest that only high-grade tumors (Hyams higher grade, less differentiated cancers or high proliferation index) might benefit from chemotherapy.

Sinonasal Primary Mucosal Melanomas

Mucosal melanomas showed a specific genomic landscape, dominated by somatic structural changes and mutation signatures different from cutaneous melanomas. Furthermore, mutations in driver genes typically associated to cutaneous melanoma, such as *BRAF*, were only rarely discovered in mucosal melanoma (approximately 10% of cases). On the other hand, *KIT* mutations occurred more frequently in melanoma arising from mucosal surface (25%) [27].

Complete surgical excision of primary lesions is the treatment of choice in localized disease, even though recurrence after surgery is very common.

Data examining the role of immune checkpoint inhibitors in the adjuvant setting of mucosal melanomas are limited. The activity of nivolumab in the adjuvant setting was explored in the phase III trial (CheckMate 238), which included a limited number of primary mucosal melanomas, and confirmed a benefit in relapse-free survival in completely resected stage III cutaneous melanomas. Accordingly, nivolumab is an attractive treatment option for patients with mucosal melanoma, within the context of a clinical trial.

In the metastatic setting, retrospective and limited experience explored the role of checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1. No randomized trial addressed the role of anti-CTLA-4 and anti-PD-1 in patients with mucosal melanomas. Evidence of ipilimumab activity was demonstrated in an expanded access program of 71 pretreated patients with mucosal melanoma [28]. An objective response rate (ORR) of 12% was observed. Furthermore, a retrospective series of nivolumab or pembrolizumab in 35 patients with mucosal melanoma, mostly pretreated, showed ORR of 23% [29]. The combination of ipilimumab and nivolumab was demonstrated to be effective in mucosal melanoma in a retrospective experience, as well, with ORR of 37% [30].

The identification of *KIT* mutations provided evidence of the role of target agents in the metastatic setting: imatinib and nilotinib confirmed durable tumor responses.

Mucosal melanomas represent a highly aggressive disease. Further efforts are necessary to better characterize the molecular features and the immune–cancer interaction: these aspects are pivotal to select patients and treatment options.

Sarcoma and Lymphoma

Up to 50 and 90 different histotypes of sarcomas and lymphomas have been described, respectively. Thus, each single entity should be regarded as an ultra-rare disease in the sinonasal tract and it is beyond the scope of this work to discuss it in single detail. We will focus here on the most common or peculiar forms of sarcomas and lymphomas and we invite the interested readers to consult other specific published reviews.

Sarcomas

Sinonasal Ewing's/peripheral neuro-ectodermal tumor (PNET) sarcomas: these neoplasms together represent up to 35% of sinonasal sarcomas and, at onset, are usually localized diseases. Treatment includes induction sequential poly-chemotherapy followed by local control with surgical resection (when possible) and RT in case of marginal resection and/or poor response to chemotherapy. DFS can reach 70–75% at 5 years [31].

Other less frequent types are undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (UPS/MFH) (12%), rhabdomyosarcoma (7%), leiomyosarcoma (6%). Again, these neoplasms require multimodal approach with anthracycline-based chemotherapy, RT and radical surgery if feasible, with DFS not exceeding 20% at 5 years [31].

Bone chondrosarcomas and osteosarcomas account for approximately 14% of sinonasal sarcomas. They are generally treated with a "sandwich" modality treatment of neoadjuvant chemotherapy, followed by surgery and by adjuvant chemotherapy with little or no response to RT. Adherence to this treatment schedule offers the highest DFS among sinonasal sarcomas [31].

Lymphomas

Primary extranodal lymphomas of the sinonasal tract display important differences in terms of epidemiology. While B-cell lymphomas are more frequent in western countries, the T/NK-cell lymphomas are more frequent in Asia and South America and are invariably EBV-related. Treatments include chemo-immunotherapy alone (anthracycline-based plus anti-CD20 rituximab for B-cell lymphomas), RT alone or, ideally, the combination of both [32]. However, in a large retrospective analysis on extra nodal B-cell lymphomas of the head and neck, the addition of RT did not add a survival advantage [33]. Non anthracycline-containing schedules are the standard for NK/T lymphomas and immunotherapy with anti-PD-1 pembrolizumab shows great promise [34].

Conclusion

Sinonasal cancers represent a heterogeneous group of disease, with different prognosis and clinical behavior. The use of systemic therapies, mainly chemotherapy, have been proven useful in selected histologies and clinical settings. Research is ongoing to better define the role of systemic treatments, which include novel targeted agents and immunotherapy.

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