Chapter 20

Patients with Rare Head Neck Cancers: Do They Need a Different Approach?

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Introduction on Rare tumors

Definition and Frequency of Rare Cancers

Rare cancers are the rare diseases in oncology needing specific approaches by the cancer community and national health systems [1]. Rare cancers are defined as malignancies whose incidence is less than 6 per 100,000 inhabitants. The reason why the definition is based on incidence and not on prevalence is, among others, that incidence does not change on other factors than frequency, i.e. not on survival. At this moment rare molecular subgroups of common cancers are not included in the rare cancers list. In absolute numbers more than 500,000 patients per year are diagnosed with a rare cancer, and 4,300,000 rare cancer patients are prevalent in Europe. The definition is widely adopted among the different scientific international societies like the European Society of Medical Oncology (ESMO) and the European Society for Radiotherapy and Oncology (ESTRO). This means that 22% of all diagnosed cancers are rare and out of the 260 cancer types identified [2], 223 (86%) are rare. The European Network for Rare Solid Cancers (EURACAN) uses this definition to create a reference network in order to improve rare cancer care (Table 20.1).

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Table 20.1 Rare cancers in the head and neck. The rate is the incidence per 100,000 inhabitants per year in Europe [2]

Tumor	Rate
Nasal cavity and sinuses	0.44
Nasopharynx	0.44
Salivary glands major/minor	1.31
Epithelial cancers of Hypopharynx	1.19
Larynx	4.64
Oropharynx	2.58
Oral cavity	3.28
Lip	1.22
Soft tissue sarcoma	0.29
Bone sarcoma	(0.8) ^a
Merkel cell	(0.13) ^a

^aThe mentioned incidences of bone sarcoma and Merkel cell carcinoma is in the whole body and not exclusive in the head and neck region

Poor Prognosis of Rare Cancers

In Europe rare cancer patients have poorer survival as compared to common cancer patients. In 2011 the 5-year overall survival of rare cancers was 49% versus 63% in common cancers [3].

Moreover, the survival of rare cancer patients in the Netherlands has barely increased over time (from 50% in 1995–2000 to 56% in 2012–2016), in contrast to the common cancers (from 59% in 1995–2012 to 72% in 2012–2016) [4].

Problems and Challenges in Rare Cancers

Common challenges posed in rare cancers are a late or incorrect diagnosis [5], less experience and a limited number of experts in the field, limited number of clinical studies (i.e., *a limited number* of phase III studies), less registered medications, a limited number of guidelines and less registries and biobanks. Patients suffering from rare cancers report higher levels of distress compared to common cancer patients due to increased anxiety and uncertainty correlated with the delayed diagnosis and feelings of isolation invoked by limited disease specific support systems [6].

Rare Cancers in the Head and Neck Region

Rare cancers of the head and neck are epithelial cancers of the larynx, hypopharynx, nasal cavity and sinuses, nasopharynx, major salivary glands and salivary-gland type tumors, oropharynx, oral cavity and lip, eye and adnexa and the middle ear. Besides these malignancies specific for the head and neck region also other rare malignancies can be located in the head and neck region, such as soft tissue sarcoma, bone sarcoma and Merkel cell carcinoma.

Phase III studies performed in the head and neck cancer field frequently include the epithelial cancers of the larynx, hypopharynx, oropharynx and oral cavity together, thereby making them 'less rare'.

Salivary Gland Cancers

Salivary gland cancer (SGC) is a distinct but heterogeneous group of malignancies comprising approximately 6.5% of cases within head and neck malignancies. This makes it a rare cancer, with an estimated age-standardized annual incidence of less than 2/100,000 in most countries. The most recent World Health Organization (WHO) classification of Head and Neck Tumors distinguishes 22 histopathological subtypes of SGC, which makes each subtype even rarer. Recognition of, and differentiation between these different subtypes is notoriously difficult and different subtypes exhibit different clinical features adding up to the complexity of the disease. For localized and resectable disease, surgical resection with or without postoperative radiotherapy is the cornerstone of treatment. In case of local recurrent or metastatic (R/M) disease, systemic treatment is challenging, but urgent given the prognosis of this disease stage. Lumped for all types of SGC with distant metastases (71% of the patients will develop recurrent/metastatic disease) the median overall survival is 15 months with overall survival rates at 1, 3 and 5 years of 54.5%, 28.4% and 14.8%, respectively. This, however, varies widely between different subtypes. For example, in adenoid cystic carcinoma median overall survival of several years in patients with distant metastases has been reported. This contrasts with salivary duct carcinoma (SDC), an aggressive subtype of SGC, in which median overall survival for R/M disease receiving best supportive care was only 5 months in the past [7].

The clinicopathological diversity of the disease justifies therapy tailored to the specific SGC subtype, highlighting the importance of adequate pathological examination (e.g. subtype, stage, growth pattern), preferably performed by a salivary gland expert pathologist. However, rarity of SGC and its extensive heterogeneity

hinders large-scale patient accrual in prospective trials and difficulties in correct histopathological subtyping of SGC endanger homogeneity of cohorts. Therefore, performance of clinical trials in SGC is challenging. This is reflected in the limited amount of studies performed with classical chemotherapeutic agents, targeted agents or immunotherapy in SGC.

Survival rates and limited benefit of chemotherapy emphasize that there is an unmet need for new therapeutic strategies for patients with R/M SGC. The paucity of treatment options may be reduced by mapping tumor characteristics and unraveling genetic aberrations in search for possible targets for systemic therapies. By doing so, SGC patients could also share in the benefits of the therapeutic advances made in more common malignancies, especially since the body of evidence for presence of such targets in different histological subtypes is increasing.

Salivary Duct Cancer (as Example)

SDC is an aggressive subtype of SGC, representing 4–10% of all SGCs. Overall survival at 3, 5 and 10-years is poor: 70.5%, 43% and 26%, respectively. Of the patients with SDC treated with curative intent, 54% will develop locoregional recurrences and/or distant metastases. In patients with distant metastases, spread to lungs (54%) and bones (46%) is seen most, and a remarkably high percentage of brain metastasis has been observed (18%). Given the dismal prognosis and high prevalence of distant metastasis, systemic therapy is often required.

The androgen receptor (AR) and the HER2 receptor (encoded by the *HER2* gene) are frequently expressed in SDC, respectively in 78–96% and 29–46% of cases. Targeting AR and/or HER2 is promising and are the best studied therapies in SDC patients.

A prospective phase 2 trial evaluating the effect of combined androgen blockade (CAB) with leuporelin acetate and bicalutamide in 36 SGC patients (of which 34 were SDC patients), showed partial or complete responses in 41.7% [95%-CI 25.5–59.2%] and stabilization of disease in 44.4% [95%-CI 27.9–61.9]. The median progression-free survival was 8.8 months [95% CI, 6.3–12.3 months] and the median overall survival was 30.5 months [95% CI, 16.8 months to not reached] [8]. Especially given the low rate of observed grade 3 or 4 toxicity, CAB plays an important role in the palliative treatment of AR positive SDC patients. Besides its role in palliative treatment, androgen deprivation therapy (ADT) may also be beneficial in the adjuvant setting. Based on retrospective data, adjuvant ADT results in significantly improved 3-year disease free survival (DFS) in patients with stage 4A AR-positive SDC (48.2% [95%-CI 14.0–82.4%] versus 27.7% [95%-CI 18.5–36.9%] in the control group who did not receive adjuvant ADT). Differences in overall survival were just below and above significance level, depending on whether or not correction for confounders was performed [9].

Trastuzumab in combination with taxane based chemotherapy is the best studied combination on HER-2 targeted therapy. Fifty-seven eligible patients with SDC were enrolled in a phase II study. The overall response rate was 70.2% (95% CI, 56.6% to 81.6%), and the clinical benefit rate was 84.2% (95% CI, 72.1% to 92.5%). Median progression-free and overall survival times were 8.9 months (95% CI, 7.8 to 9.9 months) and 39.7 months (95% CI, not reached), respectively [10]. This combination could potentially be amplified with the addition of another agent targeting HER2 (e.g. pertuzumab, lapatinib) or after progressive disease replacing trastuzumab with the antibody-drug conjugate trastuzumab-emtansine. A oral presentation at the American Society of Clinical Oncology (ASCO) in 2019 emphasizes the potential of trastuzumab-emtansine in *HER2*-amplified SGC, as 9 out of 10 patients (0–3 lines of prior treatment, median of 2) responded on this treatment. Presumably most of these patients were SDC patients. Median PFS was not reached after a median follow-up of 12 months [11]. In analogy with the positive results achieved in *HER2* positive breast cancer by adding pertuzumab to docetaxel/trastuzumab and the cases reported on this combination in SDC, this triple combination deserves a continuation in clinical studies in SDC.

Targeting *HER2* in SDC patients with *HER2* overexpression is thus promising. In patients co-expressing *AR* and *HER2* it is yet unclear whether therapy targeting *AR* or *HER2* is the best approach. However, in case of extensive or rapidly progressive disease, *HER2* targeting therapy in combination with taxane-based chemotherapy is the preferable choice over ADT.

Besides *AR* and *HER2*, a wide spectrum of mutations, is observed in lower frequencies in SDC, which altogether forms a genetic landscape highly similar to apocrine breast cancer. This includes mutations in *TP53* (53–68%), *PIK3CA* (18–26%), *HRAS* (16–23%), *BRAF* (4%) and *AKT1* (1.5%). Reports on the use of drugs aiming at these targets in clinical practice are scarce [12].

In summary, SDC has many targets amenable for systemic therapy. Elaborate mapping of tumor characteristics regarding receptor expression, genomics and pathway alterations are key to alter the dismal prognosis of patients with locally advanced or metastatic SDC.

NTRK Inhibition

Secretory carcinoma (SC), previously named mammary analogue secretory carcinoma (MASC), is a relatively new entity that was first described in the salivary glands in 2010 [13]. In retrospect, most cases of what is now called SC were initially classified as acinic cell carcinoma and also as polymorphous adenocarcinoma or adenocarcinoma NOS. SC is rare, is most often found in the parotid gland (58–68%) and behaves relatively indolent with a good prognosis. R/M disease is rare (estimated 5 and 10 years survival 95%). The genetic hallmark of SC is a

ETV6-NTRK3 gene fusion as a result of a t(12;15) (p13;q25) translocation, although other gene fusions with *ETV6* have been described (for instance *ETV6-MET* and *ETV6-RET*). *NTRK* gene fusions are known oncogenic drivers and have been described in other tumor types. This *ETV6-NTRK3* gene fusion therefore provides a promising target for systemic therapy, and the body of evidence for efficacy of TRK-inhibitors (e.g. larotrectinib, entrectinib, repotrectinib, LOXO-195) in patients with *NTRK* gene fusions is expanding. A recent phase II trial evaluating the efficacy of larotrectinib in *NTRK* fusion positive patients included 12 patients with recurrent or metastatic (MA)SC and reported a response rate of 75% and the median progression free survival was not reached after median follow-up of 9.9 months [14]. Responses in patients with (MA)SC have also been observed for entrectinib and repotrectinib. A phase I/II trial evaluating LOXO-195 in second line is currently recruiting and is open for inclusion of *NTRK* fusion positive SGC patients previously treated with a TRK-inhibitor (NCT03215511).

Whether *NTRK* gene fusions are present in other subtypes of SGC is currently unknown, but treatment with TRK-inhibitors is a very promising treatment option, an option that should be investigated in all SGC patients with advanced disease.

Future

Patients with rare cancers deserve a different approach. Only then we can make progress to improve care and cure in rare cancers.

In the rare cancer agenda 2030 written by the Joint action on Rare Cancers (JARC) ten recommendations are made [1]. In rare cancers networking is crucial; this means that networking with patients, in health care systems, but also in medical education is extremely important. Furthermore, regulation on rare cancers should tolerate a higher degree of uncertainty, which means that the ‘rules’ we made for registration of new medications in common cancers (mostly based on phase III evidence) cannot be the same for rare cancers.

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