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Article

Principles of Specific Treatment and Palliative Care in Advanced Head and Neck Cancer

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Abstract: Most head and neck cancers are diagnosed in advanced stages, when the curative interventions are no longer possible. The assessment and the multidisciplinary therapeutic approach of the locally advanced cases are difficult since the onset of the disease becomes a significant challenge for the whole attending team (including both the patient and his family) because they have to deal with to an extensive symptomatology (abundant secretions, refractory pain, mutilations predominantly in the cephalic area), with the cure of stomas (tracheostomy, gastrostomy) and with various post-therapeutic sequelae. The present paper reflects the impact of late diagnosis, the complexity of the multimodal specific oncological treatment (chemotherapy, radiotherapy, immunotherapy, palliative and terminal treatment), the adaptation of medical care to the psycho-emotional structure, having as an example the case of 54-year old patient (with his consent) diagnosed with pharyngolaryngeal neoplasm who presented himself to "St. Luca" Chronic Disease Hospital, the Oncology-Palliative Care Department, in September 2021. In patients with locally advanced head and neck cancers, besides the specifically oncological therapeutic decisions, the empathic-emotional connection between the medical team with the patient and his family plays a key role in the therapeutic conduct.

Keywords: head and neck cancer; multidisciplinary therapeutic approach; palliative care

1. Introduction

Head and neck cancers represent a heterogeneous category of locations, which comprises: the oral cavity, the hypopharynx, the oropharynx, the nasopharynx and the larynx. The early diagnosis is the most important prognostic factor, but unfortunately, only 30-40% of all cases are diagnosed in the early stages of the disease. Most cases are diagnosed in advanced stages, when the curative interventions are no longer possible. Head and neck cancers represents the sixth cause of cancer worldwide [1–5].

The low survival rate (10-25% at 5 years for advanced and metastatic stages) is determined by both the late diagnosis and the inefficiency or the failure of the prevention methods, as the main risk factors for this disease are well-known: smoking, alcohol, the “fatal” combination between smoking and alcohol, the infection with papillomaviruses. Overall survival is worse with EGFR amplification present in laryngeal squamous cell carcinoma (SCC) compared with oral SCC. Significantly higher rates of amplification of the 3q26 locus have been reported in laryngeal SCC compared to oral SCC [6]. Also, high stromal tumor infiltrating lymphocytes (TIL) assessed in hematoxylin-eosin sections and CD3+, CD4+, and/or CD8+ intratumoral and stromal TIL could predict better clinical outcome [7]. Even after a specific treatment with a complete remission, 30-60% of the patients diagnosed in advanced stages will have an evolution of the disease either through local-regional relapse or through metastasis [1,6–9].

That being said, this paper will focus on the assessment and the multidisciplinary therapeutic approach of the locally advanced cases since the onset of the disease.

The pre-therapeutic assessment comprises: a complete Ear, Nose, Throat (ENT) examination, a biopsy, a computed tomography (CT) (head, cervical region, thorax, abdomen) and Positron Emission Tomography (PET-CT), the assessment of the nutritional, psycho-emotional state (speech impairment, swallowing impairment). Thus, a multidisciplinary team formed by an otorhinolaryngologist, a chemotherapist, a radiotherapist, a surgeon, a specialist in palliative care, a specialist in nutrition and a psychologist is required [1,10–15].

The therapeutic indication is established after the arrival of the histopathological result (approx. 90% of the cases being squamous cell carcinomas), after stage determination and, of course, with the patient's consent. For example, there may be cases, in which the patient expresses the desire for concomitant chemo-radiotherapy, being thus detrimental to surgery [12,13,15–17].

2. Materials and Methods

We report the case of a 54-year male patient, presented to the ENT Hospital “Prof. Dr. Dorin Hociotă” in September 2021 for an invasive pharyngolaryngeal keratinizing squamous cell carcinoma (SCC), treated in “St. Luca” Chronic Disease Hospital, the Oncology-Palliative Care Department (chemotherapy, immunotherapy and palliative care), The Oncological Institute “Prof. Dr. Alexandru Trestioreanu” (radiotherapy) and Surgery Department of Clinical Emergency Hospital “Bagdasar-Arseni” (insertion of a feeding gastrostoma), from Bucharest, Romania.

3. Results

A 54-year male patient, a heavy smoker and an ethanol user, presented to the ENT Hospital “Prof. Dr. Dorin Hociotă” in September 2021 for odynophagia, progressive dysphagia, otalgia, symptoms that started approximately 6 months earlier. The ENT examination revealed a lateral-cervical tumor formation of 5/3 cm, rough, immobile, adherent to the deep and superficial planes, painful spontaneously and upon palpation. The endoscopic laryngeal examination revealed an infected keratinized infiltrated into vegetation tumor formation, which comprises the right piriform sinus, including the lateral and posterior pharyngeal wall.

A trans-isthmus (thyroid isthmus) tracheostomy was performed between the second and the third tracheal rings (T2-T3), with the insertion of a tracheal cannula, and collection of multiple biopsy fragments from the pharyngolaryngeal tumor. The symptoms improved under treatment with antibiotics, anti-inflammatory drugs and analgesics. The ENT doctor considers that surgery is inappropriate, for which reason he refers the patient to the oncology department after finding out the histopathological result, in order to determine the therapeutic approach. The histopathologic result revealed: an invasive keratinizing SCC, G1 grading.

The patient presents himself at “St. Luca” Chronic Disease Hospital, the Oncology-Palliative Care department, where a CT scan was recommended for stage determination, which revealed: a right hemi-hypopharyngolaryngeal tumor of 3.3/ 2.3/ 7 cm, with an important luminal obstruction, with the absence of visualization of the right vocal cord, with the infiltration of the posterior commissure, lysis in the laryngeal cartilage, which is in posterior proximity to the paravertebral

muscle in the C5 and C6, a right hemi-opharyngeal tumor of approximately 2.5/ 2.6/ 4.1 cm, with the infiltration of the right lateral oropharyngeal hemiwall and the right hemibase of the tongue, right supra- and subhyoid laterocervical adenopathy of 2.1/ 1.4 cm and 3.4/ 2.3 cm respectively, without secondary determinations at the cerebral, pulmonary and abdominal level Tumor, Node, Metastases – TNMc: T4a, N2, M0 - stage IV A.

Clinically, the patient presents a performance status of 2 to 3 on an Eastern Cooperative Oncology Group (ECOG) scale and a moderate general state due to a major pain syndrome in the right ear, the laterocervical area, with a score of 8 on the numerical pain assessment scale, requiring the initiation of the third-degree analgesic medication, with a major slow-release opioid, Oxycodone 20 mg, one tablet every 12 hours, orally and Morphine sulfate with rapid release, 10 mg, one tablet administered at 6-hour intervals, orally.

The case is discussed by the multidisciplinary commission formed by a chemotherapist and a radiotherapist, who recommend the initiation of a systemic treatment, and a reassessment after 4 series. The systemic treatment with taxane and platinum salts is initiated (docetaxel + cisplatin), a treatment that was well tolerated during the 4 cycles, except for the occurrence of progressive anemia, without iron deficiency, folate, B12 deficiency, for which a treatment with erythropoietins, with the maintenance of hemoglobin at a level of approximately 10 mg/dl.

Clinically, the performance status of the patient is maintained, without any improvement or worsening, with a controlled pain syndrome, but with the occurrence of refractory constipation despite the prophylactic treatment administered as a prophylactic measure. Thus, the opioid “switch” was attempted, with the switch to transdermal Fentanyl patch with sublingual tablets of fentanyl, for the break-through pain phenomena. Fentanyl is known as being a less important factor in constipation than other major opioids.

After the 4 series of chemotherapy, a reassessment is done at the radiotherapy department within the Oncological Institute in Bucharest. The patient is admitted to the radiotherapy department where an ENT consultation and a cranial-cervical-thoracic CT is performed. The ENT clinical examination reveals a stenotic tracheal stoma, an infiltrated vegetative tumor at the base of the tongue, lateral and posterior pharyngeal wall, right piriform sinus, right aryepiglottic fold.

The CT reveals a bulky tumor at the base of the tongue/ floor of the mouth, the right tonsillar and epiglottis lodge with central necrosis, in dimensional progression compared to the previous examination; at the pulmonary level: areas in ground glass bilaterally, most likely after a recent infection with SARS Cov-2, a lytic bone lesion at the T1 level. Between January 5th and January 18th of 2022, the patient underwent external conventional radiotherapy with photons, for palliative purposes, up to the total dose of 30 Gy (10 fractions, 3 Gy/ fr, 1 fr/day) with a target volume for tumor masses at the base of the tongue, hypopharynx, larynx, T1-T2 vertebrae, with a good tolerance. The ENT examination upon discharge revealed a minimal improvement compared to the previous examination, with root mucositis lesions. During his admission to radiotherapy, the patient underwent an infectious disease consultation with a bacteriological balance performed (exudate, tracheostoma culture), with the result of Methicillin-resistant *Staphylococcus aureus* (MRSA), a consultation after which the initiation of a treatment with antibiotic and antimycotic drugs was recommended.

It is worth mentioning that the patient constantly refused the insertion of a feeding gastrostoma, despite the insistence of the medical staff and of the family, despite the fact that he was explained the risks, the possibility for difficulty in swallowing, and even the progressive inability to swallow.

The patient returns to the Oncology Department of “St. Luca” Hospital for reassessment after one month. His general condition is affected by severe fatigue, an ECOG3, mucositis and radiation induced edema (an ENT examination in February 2022), with the occurrence of polyneuropathy (especially at the level of the fingers), most likely neuropathy secondary to the oncological treatments, and the recurrence of the major pain syndrome, for which reason the resumption of a specific treatment is delayed, a palliative symptomatic treatment being recommended instead. A nonsteroidal and steroidal anti-inflammatory, diuretic treatment is initiated, a drug from the gabapentinoid class for the neuropathic pain is added, along with a selective inhibitor antidepressant

for regaining serotonin – fluvoxamine maleate, the dose of the fentanyl patch for nociceptive pain is increased, rigorous cleaning of the oral cavity is recommended, by using mouthwash with benzidamine, the used of a local topical anti-inflammatory is recommended, with the significant improvement of the symptoms. At the same time, the patient undergoes psychological counseling and occupational therapy.

One month and a half after the completion of radiotherapy, the patient presents with significant hemorrhage with oral externalization also at the level of the tracheal cannula, for which reason he is admitted to the ENT hospital, where, after a hemostatic, antibiotic, analgesic, erythrocyte mass treatment, he presents a favorable evolution, without any recurrence of bleeding, with normal breathing on the tracheal stoma.

The oncologist attending the patient recommends a CT scan to be performed (April 2022), which reveals the stationary primary tumor, without newly occurred lesions.

Taking into account the progression of the disease after the regimen of chemotherapy based on platinum salts through the occurrence of the osteolytic lesion and the dimensional progression of the tumor formation, according to the desire of the patient and his family, with a slightly deteriorated performance status along the evolution associated with a progressive weight loss, the initiation of immunotherapy with Nivolumab for recurrent and metastatic disease is decided upon.

After 4 administrations at a 2-week interval, immunotherapy is discontinued because of the worsening of the general condition through dysphagia for solid food, significant weight loss with the occurrence of cachexia, significant fatigue, and major pain syndrome. The patient is finally convinced to agree with the insertion of a feeding gastrostoma. The intervention was performed at Surgery Department of Clinical Emergency Hospital “Bagdasar-Arseni”, Bucharest. Unfortunately, it was too late. This will have a palliative role in order to prolong the short survival left. He remains hospitalized in the Palliative care department for 2 months, with a slow evolution to emaciation (29 kilos at the time of death), with aphasia, immobilized to the edge of the bed and subsequently to bed, with gastrostomy nutrition, with control of the pain syndrome through increased doses of injectable morphine (30 mg every 6 hours – one vial + ½ every 6 hours).

He dies in September 2022, one year after the diagnosis was made.

4. Discussion

We presented an extremely complex clinical case of pharyngolaryngeal SCC, which underwent all the therapeutic stages, a case which was affected by a wide range symptomatology, related both to the disease and to the adverse reactions of the treatments, a case which experienced ups and downs from all points of view: physical, psycho-emotional and social [11,13,15].

This patient's case is an example of how important a multidisciplinary collaboration is in making the choice of the best treatment option, of how important the aspects of a correctly applied palliative care from the onset of the disease are in locally advanced and metastatic cases [10–15].

Regarding the systemic chemotherapy, the regimen of choice was based on taxane and planinum salts.

Induction chemotherapy can be a good choice in cases in which the patients are eligible for radiotherapy.

Regarding the radiotherapy the patient underwent external conventional radiotherapy with photons, for palliative purposes.

Palliative radiotherapy is indicated when the curative-intended treatment is not possible, for the prevention of the control of local symptoms. Variants of regimens: 30 Gy in 10 fractions, 40 Gy in 10 fractions, 40-50 Gy in 16 fractions [16,17].

Regarding the 2nd line regimen, immunotherapy with Nivolumab was the regimen of choice.

More than 50% of the patients will experience recurrence or metastasis after the curative intention treatment. These cases require the continuation with a systemic treatment. The standard regimens for 1st or 2nd line systemic treatment comprise:

For patients who have undergone platinum salt chemotherapy in the last 6 months: nivolumab/ pembrolizumab/ cetuximab/ taxane/ methotrexate.

Pembrolizumab has proven efficient for programmed death ligand 1 (PDL-1) positive patients, with a higher survival rate: 14.9 months versus 10.7 months, and also with a lower rate of adverse effects of the treatment [13,18–20].

Nivolumab has revealed an increase in the overall survival rate compared to standard chemotherapy alone: 7.5 months versus 5.1 months [19,21].

In addition to its use in recurrent disease and/ or metastasis, there is currently intensive research regarding the introduction of immunotherapy as concomitant therapy for advanced local-regional disease.

As immunotherapy exerts a synergistic effect with chemotherapy on the immune response, there are ongoing studies related to a similar effect of concomitant radiotherapy +/- standard chemotherapy.

As an adjuvant treatment, there are ongoing studies related to the association of an anti PDL-1 (pembrolizumab, nivolumab, durvalumab) agent with an anti-Cytotoxic T-Lymphocyte-Associated protein-4 (ipilimumab, tremelimumab) agent [19,21,22].

Regarding palliative care, in the advanced stages of the disease, palliative care plays a very important role in the management of patients with head and neck cancer [16,17,22].

The most common disorders these patients have are mucositis, the pain syndrome, speech related disorders, swallowing and eating impairment, which affect their body weight, emotional disorders with a difficult compliance in accepting some necessary invasive procedures, such as gastrostomy or tracheostomy.

These situations affect their self-esteem, with the risk of neuro-psychological symptoms such as anxiety or depression [4,11,14].

The involvement of palliative care as soon as possible after the diagnosis has a positive impact on treatment compliance, and therefore, on the overall survival rate, as well as on maintaining an optimal life quality.

Oral mucositis is an inflammation that occurs in the oral cavity and oropharynx and it is characterized by erythema, edema, atrophy, which may progress to ulceration.

The mechanism of action of some chemotherapeutic agents causes hyperplasia, dysplasia, atrophy, glandular or collagen degeneration at localized or diffuse ulceration. The most affected areas at the level of the non-keratinized mucosae, the destruction of the epithelial layer leads to the exposure of the connective tissue and the stroma with nervous terminations, thus leading to severe pain in the oropharynx.

The chronic effects of radiotherapy to the head and neck comprise soft tissue fibrosis, the slowing down of the healing processes of the ulcerations, of the ulcerations at the site of dental extractions. Fibrotic changes in muscles of mastication of the temporo-mandibular joint may occur one year after the completion of radiotherapy.

The main complications of mucositis are xerostomia and oropharyngeal pain. During and after radiotherapy, the degree of severity of xerostomia is generally directly proportional with the dose and the area of the salivary glands exposed in the treatment field.

Xerostomia is associated with the alteration of life quality through changes in taste, difficulty speaking and swallowing, being a favorable factor for the occurrence of bacterial colonies as well.

Oral candidiasis is very common, being associated with angular cheilitis (an inflammation of the oral commissures). Antimycotic drugs are used: sprays (clotrimazole, mycostatin), and in case of chronic refractory candidiasis, a prolonged treatment with an oral antifungal preparation is necessary: fluconazole, ketoconazole, amphotericin. Prevention is part of the therapeutic approach (vitamins E, C), amifostine, glutamine, cryotherapy, laser therapy [1,9,16,17].

Despite the fact that radiotherapy is an effective oncological treatment in head and neck cancers, patients often enter a vicious circle due to pain, dysphagia, aspiration, malnutrition which are directly or indirectly caused by it, which leads to a decrease in life quality, treatment compliance, oral feeding with the need for feeding gastrostomy, increase in the number of hospitalization days, interruption of the specific treatment with a negative impact on disease control.

There is no exact consensus regarding the therapeutic approach of the pain caused by mucositis. This is more common than other primary locations, and it can be severe, sometimes debilitating.

The standard conduct is the use of major opioids, but solutions for dose reduction through multimodal analgesic therapy are being sought. Its principle of use is the combination of various classes of drugs with different mechanisms of action, the goal being optimal pain control, the avoidance of major opioid medication, and thus, the reduction of their adverse reactions [23–25].

Pain due to radiotherapy-induced mucositis is multifactorial and it comprises: a nociceptive component (somatic and visceral) which occurs through direct damage to the mucosa, and a neuropathic component that occurs through tumoral infiltration or through chemotherapy/radiotherapy induced polyneuropathy. It is important to determine the etiology, since neuropathic pain is less responsive to analgesic drugs with major opioids. For this situation, drugs from the class of gabapentinoids, such as gabapentin, pregabalin are particularly preferable. Moreover, there is a class of drugs that seems to have a synergistic action with the opioid medication used for nociceptive pain, by potentiating its effect. Non-steroidal anti-inflammatory drugs (NSAIDs) play a role against the inflammatory response induced by radiotherapy. There is a synergism with both acetaminophen and the opioid medication [25].

After some studies have been undergone, it seems that multimodal analgesic therapy may become the now gold standard in the treatment of pain caused by radiotherapy-induced mucositis. This implies the association between NSAIDs + acetaminophen + pregabalin +/- opioid [26].

Palliative care refers to all components that contribute to life quality, so from the onset of the disease, these patients must be advised nutritionally, psychologically, the goal being the prevention of a vicious circle occurrence: malnutrition, depression, anxiety which may lead to a poor performance state, lack of good compliance, which in turn may lead to the discontinuation of the specific treatment [4,9,11,14].

5. Conclusions

It is not much to say in order to describe what the patient went through throughout the evolution of his disease. A young patient, with a long-life expectancy, who clung to life until the end, and for whom the multidisciplinary team made all the necessary efforts to make the optimal decisions. It is a situation in which the attending team was formed by many doctors (an ENT specialist, a chemotherapist, a radiotherapist, a surgeon, an infectious disease doctor), a psychologist, nurses/paramedical personnel (nurses' aides, orderlies) who paid extra attention on a daily basis, especially in the last two months of the patient's life. It is not an easy thing to care for a patient with gastrostomy, tracheostomy, aphasia and immobility. Moreover, another team was made up of his family, who provided all the support he needed.

The main conclusion of this paper, both for the theoretical and the practical part, is that this pathology represented by head and neck cancers is a resonant one for some very complex subjects, that in order to optimize the maximum success that can be achieved, there must be a good collaboration between clinicians, a collaboration that must combine both the scientific part related to the oncological treatments and the empathic, emotional part. The famous expression "sometimes it is the quality of life that matters, and not the quantity" is not accidentally expressed.

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Informed Consent Statement: Written informed consent for participation in the study, histopathologic preparation of the tissues and for publication of this paper was obtained from the family of our deceased patient.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding authors.

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