Case report

Nasopharyngeal carcinoma – treatment possibilities in patients with primary metastatic carcinoma

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ABSTRACT

This article presents methods of effective treatment of primary metastatic nasopharyngeal carcinoma, both causative and symptomatic, taking into account possible available treatment therapies (chemotherapy, targeted therapy, radiotherapy), and includes a case report. The applied treatment allowed for satisfactory control of the disease and much higher overall survival than expected – the patient survived for 53 months from the initial diagnosis and 41 months from being diagnosed with metastatic carcinoma.

Key words: nasopharyngeal carcinoma, strategy of treatment, systemic therapy

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a rare disease in Poland compared to the endemic areas of East Asia, North Africa, and the areas of the Mediterranean Basin. The frequency of its occurrence in Caucasians is 0.2/100,000. In Poland, around 150 new cases are reported annually [1, 2].

According to WHO, there are three subtypes of NPC:

- type 1 – squamous cell keratinised carcinoma
- type 2 – differentiated non-keratinised carcinoma
- type 3 – non-differentiated non-keratinised carcinoma.

Initial development of nasopharyngeal carcinoma is not accompanied by any symptoms, and no specific symptoms are present at early stages of tumour growth. The time which elapses from the first clinical symptoms to a diagnosis is on average 8–10 months. The most common clinical symptom in most patients is cervical lymphadenopathy [3].

Epstein–Barr virus (EBV) plays the most important role in the pathophysiology of type II and III nasopharyngeal carcinoma [4, 5]. Type I is the most common in regions with low morbidity [6]. NPC is biologically different from other squamous cell carcinomas of the head and neck. Non-differentiated carcinoma is diagnosed in 95% of patients with NPC, and is characterised by frequent metastases to regional lymph nodes, distant metastases to the bones, and, the least frequently, to the lung [7, 8].

In the case of early and regionally advanced carcinomas, a first-line therapy is radiotherapy or, more frequently, chemotherapy. A basic therapy used in the treatment of metastatic nasopharyngeal carcinoma is chemotherapy. Clinical studies show that the cisplatinum based treatment results in response of 50–70%, but advantages are short-term, lasting usually 6–9 months [9].

In Europe, relative yearly survival in patients diagnosed with NPC is 76%, and a 5-year survival rate is 50% [10, 11]. Distant metastases and regional recurrence are the most common causes of deaths in patients with NPC [12]. Metastases occur most frequently in the bones, and frequently in the lungs and in the liver. The median survival in patients with metastatic NPC is 8 months [13]. This work presents a case of a man diagnosed with type III nasopharyngeal carcinoma, originally metastatic, who survived 53 months due to the applied therapy.

CASE STUDY

A patient, aged 34, reported to the general surgery clinic in August 2009 due to the palpable mass in the left supraclavicular fossa present reportedly for about 2 weeks. Smoker (15 pack-years). No history of chronic diseases or cancer. Upon examination, the patient was in a very good general condition. The examination revealed a 4 × 3 cm lymph nodes mass in the left supraclavicular fossa, moving on its ground very slightly. Diagnostic tests with lymph node biopsy, and PET/CT were ordered. Histopathological examination of the material biopsied from the cervical lymph node revealed metastatic non-differentiated nasopharyngeal carcinoma (immunohistochemical examination: EMA+, CK19+, EBV+). The cancer was originally located in the nasopharynx as shown by PET/CT (27.08.2009), with secondary lesions in the tonsils, cervical lymph nodes, and the supraclavicular lymph nodes on the left. Disease stage per TNM 7th edition: CS IVB.

Induction chemotherapy was administered in September 2009 per 2 × PF regimen (cisplatinum and 5-FU), resulting in partial response. Combined radical chemotherapy and radiotherapy were administered (70 Gy/35 fraction on the nasopharynx area, and the area of the swollen cervical lymph nodes; 63 Gy/35 fraction on the elective area of the cervical and supraclavicular lymph nodes combined with cisplatinum). The applied treatment resulted in full remission of the original lesion and the lymph node lesions.

After 9 months, progression of the disease was observed in the bones, i.e. the cancer spread to the L3 vertebra, and palliative radiotherapy was administered (20 Gy/5 fraction).

Imaging performed in September 2010 showed disease progression in the lymph nodes (mediastinal, supradiaphragmatic on both sides, right subphrenic, left periaortic, internal iliac on both sides), and new lesions in the bones (right iliac bone and right inferior pubic ramus). Palliative chemotherapy regimen of 6 × PF was administered (5-FU and cisplatinum). Palliative radiation was applied (20 Gy/5 fraction) to the lesion area in the right pubic bone and ischium. Examinations performed in March 2011, after treatment cycle, showed regression of the lymph node lesions.
From August to December 2011, due to the progression of the disease in the mediastinal lymph nodes and in the retroperitoneal space, docetaxel was applied (6 × as a monotherapy), resulting in partial regression.

Another progression of the disease was in March 2012 in the mediastinal and retroperitoneal lymph nodes, and in the bones

– Th3 and L3 vertebrae, sacrum, and humerus. This time, palliative immunochemotherapy was administered as part of the treatment. From May to October 2012, combined therapy was applied (6 × PF + cetuximab, and, subsequently, cetuximab as a monotherapy until February 2013). Again, partial response was observed.

In March 2013, progression was observed in the non-regional lymph nodes. Palliative chemotherapy was applied as per regimen 6 × PG (cisplatinum and gemcitabine) resulting in partial remission.

In January 2014, CT scan revealed disease progression in the mediastinal and retroperitoneal lymph nodes. The patient was scheduled for palliative chemotherapy (paclitaxel 80 mg/m^2 every 7 days). After 4 months, the treatment was assessed based on a CT scan of the abdominal cavity, pelvis minor, and thorax. The condition was assessed per RECIST as stable (25% regression in lymph nodes). Tolerance to the treatment was good and so it was resolved that it would be continued.

In July 2014, the patient complained of more acute pain in the lumbar spine. LS spine MRI was performed, showing new lesions indicating active metastatic foci. Photon radiotherapy was administered (21 Gy/7 fraction was applied to the lesions in L1-L3).

In August 2014, a CT scan revealed lesions in the liver, most probably metastatic, lymphadenopathy in the abdominal cavity and pelvis minor lymph nodes, and osteoblastic foci in the vertebral bodies of the lumbosacral spine. The patient's overall condition was fairly good (WHO: 1 without significant deviations in lab tests). In September 2014, palliative chemotherapy was commenced per PG regimen (cisplatinum and gemcitabine). Due to haematological complications in the form of anaemia (CTCAE 4) and thrombocytopenia (CTCAE 4) occurring after the first treatment cycle, it was resolved to change to gemcitabine monotherapy.

After 3 months of the therapy, a CT scan revealed disease progression with numerous new lesions in the liver, peritoneal cavity lymph nodes, and the bones. In addition, pericardial effusion and fluid in the pleural cavity were present. The patient's overall condition worsened. It was resolved to end systemic treatment. In January 2015, after 5 years of fighting the disease, the patient died.

DISCUSSION

Frequency of the NPC occurrence outside endemic regions increases with age [6]. Epstein–Barr virus infection is here the biggest risk increasing factor. In addition, a diet rich with salty fish plays a significant role in the occurrence of the disease: the cancer is the most common in East Asia where salty fish is eaten as a basic food. Other risk factors include consumption of preserved food, cigarette smoking (more linked with type I NPC), and chronic respiratory diseases [14–17].

The case presented is of a young patient without any significant factors increasing the risk of NPC apart from the probable EBV infection and nicotine addiction.

Median survival in patients with metastatic NPC is 8 months (if the disease affects the skin and the lymph nodes below the collarbone, the median is 20 months, for bones only it is 6.5–8 months, liver – 3.8–5.4 months). Longer survival rates are observed very rarely [13, 18].

The patient described survived for 53 months from an initial diagnosis and 41 months from the time when the cancer spreading to the bones was observed. Several factors indicated a possibly long survival. According to the literature, adverse prognostic factors are female gender and the disease spreading to the liver. The patient described was a man and metastases to the liver were observed only after 4 years of being diagnosed with NPC. Positive prognostic factors in the case of NPC are an age below 44 years upon diagnosis, good response to a radical therapy, no relapse for more than 6 months, and no regional recurrence from the end of radical treatment [12, 13]. All these factors occurred in our patient.

NPC is a radiosensitive cancer, and, therefore, radiotherapy is applied as a standard procedure for all early and locally advanced carcinomas. In the case of rare carcinomas, such as NPC, the best treatment regime is hard to develop. A first-line therapy in the majority of patients is chemoradiotherapy combined with cisplatinum. In the case of patients with the first stage of cancer development, radiotherapy alone can be administered. For the second stage, chemotherapy is recommended to avoid distant metastases, however, randomized studies into the subject are absent [19, 20]. Limited recurrence is potentially curable, and the main problem is the choice of an appropriate therapeutic option from radiotherapy, brachytherapy, surgical resection, and the possibility of adding systemic treatment. In the case of metastatic NPC (stage IV C), only palliative therapy is an option. Treatment based on platinum derivatives is usually used as a first-line therapy since cisplatinum was proved to be the most effective drug [20]. Randomised clinical studies have shown that the most effective form of systemic treatment is a polytherapy with PF reg-

imen being a recommended combination [19]. Other cytostatic drugs with proven effectiveness are paclitaxel, docetaxel, gemcitabine, irinotecan, doxorubicin, and oxaliplatin [9, 19–22]. Most commonly, the treatment includes two lines of palliative chemotherapy. Another drug with anti-cancer activity against squamous cell carcinomas located in the head and neck is cetuximab. The drug is an IgG1 monoclonal antibody against the epidermal growth factor receptor (EGFR), able to destroy it, not commonly used in the treatment of NPC [23]. EGFR is present in the majority of human cancers of epithelial origin, and is associated with more aggressive development, resistance to treatment, and a worse prognosis [24]. EGFR is present in over 85% of NPC cases [25]. Biological therapy is used more and more frequently in the treatment of non-keratinizing NPC, particularly in the case of failures or recurrences, although there are no randomized clinical studies proving the effectiveness of such procedure [26]. The initial radical treatment regimen applied in the case of the above patient was compliant with recommendations. The 2 × PF induction chemotherapy and chemoradiotherapy brought about the desired effect resulting in full regression. Upon observing distant metastases, due to their location (L3 vertebra), radiotherapy was applied which was then followed by palliative chemotherapy (6 × PF). Even though no standard procedure was applied after progression subsequent to the first line of palliative chemotherapy, it was resolved to continue the therapy due to the very good overall condition of the patient, and good response to the treatment.

The patient in question was treated with 5 lines of palliative chemotherapy and one line of immunochemotherapy. It must be clearly stressed that despite being treated with cytostatic drugs for such a long time, the patient's treatment tolerance was very good, and there was no significant worsening in the quality of the patient's life, except for the last stage of the disease.

It must be noted that in the case of the described patient, apart from the survival time, disease progression occurred in similar time intervals. Usually, in the case of long-term treatment of metastatic carcinoma, remission periods become shorter with time. The disease stability and good response to treatment observed in this case are not typical of metastatic NPC (tab. 1).

TABLE 1.
Administered therapies, response to treatment, and time to progression.

Treatment line	Type of treatment	Response to treatment	Time to progression (months)
1st	6 × cisplatinum + 5-fluorouracil	PR	10
2nd	6 × docetaxel	PR	8
3rd	6× cisplatinum + 5-fluorouracil + cetuximab (supportive)	PR	11
4th	6 × cisplatinum + gemcitabine	PR	11
5th	6 × paclitaxel (monotherapy)	SD	7
6th	1 × cisplatinum + gemcitabine followed by gemcitabine as a monotherapy	PD	6

PD – progression of disease; PR – partial response; SD – stabilization of disease.

CONCLUSION

The question is what steps to take with very limited standard procedures, or in their absence. In Europe, a disease is considered rare if it affects less than 5 persons per 10,000 [27]. In the case of diseases where it is difficult to obtain a large enough study group and conduct clinical trials, which could help to develop the most efficient standard procedures, attention should be paid to doctors demonstrating an individual approach to patients. An issue frequently discussed by medical practitioners, not only oncologists, is whether there is a justification for creating centres intended for the treatment of rare diseases. A disease, including NPC, may be rare in one region and common in another. Bearing the above in mind, it is sensible to bring a larger number of patients with a specific disease to one centre. It would allow for clinical studies to be conducted, procedure recommendations to be developed, clinical experiences to be exchanged between doctors, and specialist personnel to be trained [28].

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