The Therapeutic Options Indicated in Malignant Pheochromocytoma: About A Single Case

O. Zouiten¹, N. Elbouardi², L. amaadour¹, K. Oualla¹, Z. Benbrahim¹, S. Arifi¹, N. Mellas¹
¹(Department of Medical oncology / University hospital center Hassan II-FEZ, Morocco)
²(Department of radiology / University hospital center Hassan II-FEZ, Morocco)
Corresponding Author: O. Zouiten

Abstract: The pheochromocytoma is a rare tumor. Loco regional extension and the presence of metastasis define the malignant pheochromocytoma. We reported a case of a 45-year-old female patient having unresectable pheochromocytoma relapse with local extension and diaphragmatic and lymph node metastasis treated by chemotherapy and target therapy with therapeutic failure. The objective of our publication to make a review for the therapeutic options indicated in malignant pheochromocytoma.

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I. Introduction

Pheochromocytoma (PHC) is a rare tumor. The metastatic character is found in about 20% of cases. The malignant nature of this tumor is determined by the presence of metastases. Therapeutic management is essentially based on chemotherapy, metabolic radiotherapy, and targeted therapy.

II. Case Presentation

We report the case of a 45-year-old female patient, with no particular antecedents who consulted for lower back pain with hot flashes and recurrent sweating. The radiological assessment showed an adrenal mass. She had a right adrenalectomy showing a pheochromocytoma.

Three years later, the patient consulted for the same symptomatology with left lumbar pain. The radiological assessment revealed the presence of a left adrenal mass (Figure 1). Surgical exploration revealed an adrenal tumor, the invasion of neighboring organs and the presence of diaphragmatic metastases, whose biopsy confirmed their secondary origin.

After admission to the department of medical oncology of fez the clinical examination finds a patient in good general condition with an index of Karnofsky > 80%, not arterial hypertension, a painful mass of the left hypochondrium measuring 5 cm. The dosage of urinary catecholamine was normal.

Cyclophosphamide-Vincristine- Dacarbazine chemotherapy has been indicated. After the first 03 cures, a stability of the tumor mass with a progression of the tumoral disease in lung.

A second therapeutic line based by Sunitinib was administered. After 3 months of treatment. The clinical and radiological evaluation notes a great progression of the metastatic disease (Figure 2). One month after the patient died.

III. Discussion

Pheochromocytomas are rare tumors with poor prognosis.

Malignancy is defined by the presence of a large tumor size, where an ectopic site, where excessive excretion of dopamine where the invasion of the capsule and neighboring organs. In fact, only the presence of lymph node metastases or remotely asserts the malignancy; histological examination does not provide definite information.

Histopathological, biochemical, molecular and genetic markers provide only information on the potential risk of metastatic spread. Large size, extra adrenal localization, dopamine secretion, SDHB mutations, PASS score greater than 6, high Ki-67 index are potential cancer indices.

Metastases may be present at first diagnosis or occur years after primary surgery. The measurement of plasma and / or urinary metanephrine, normetanephrine and metoxytyramine is recommended for biochemical diagnosis.

Anatomical and functional imaging using different radionuclides is necessary for tumor localization and metastasis.

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**Chemotherapy (Table 1)**

Chemotherapy was the first therapeutic option used in pheochromocytomas. The use of streptozocin in two patients with inoperable pheochromocytoma was unsuccessful morphologically and even biochemically (1), whereas partial biochemical remission and a 25% reduction in adrenal mass and a 50% reduction in hepatic metastasis was observed later in a single case. (2). Combined chemotherapy with streptozocin, cyclophosphamide and 5-fluorouracil resulted in a slight biochemical improvement of the disease (3).

A new, more efficient protocol was introduced in 1985 by Keizer et al. (4), who used a combination of cyclophosphamide, 750 mg / m2 body surface on day 1; vincristine, 1.4 mg / m2 on day 1; and dacarbazine 600 mg / m2 on days 1 and 2. In 1988, these researchers published a non-randomized study of 14 patients with metastatic pheochromocytoma and receiving this treatment (5). Two patients had a complete tumor response and six had a partial tumor response with a median duration of 21 months. A biochemical response was documented in 11 patients (median duration: 22 months). A number of case reports subsequently confirmed the short-term benefits and tolerable side effects of the CVD protocol; however, a recurrence occurred within 2 years in most of these patients (6).

Different chemotherapy protocols have been tested in a small number of patients. One patient had a reduction in the use of antihypertensive after a combination therapy with cisplatin and 5-fluorouracil (7). A combination therapy of anthracyclines with modified CVD therapy has been shown to be effective in case of pheochromocytoma with distant lymph node metastases, with continuous remission 3 years after discontinuation of chemotherapy (8). A radiological response was reported in one of three cases of metastatic pheochromocytoma in 29 patients with neuroendocrine tumors treated with an oral regimen of temozolomide and thalidomide (9).

Contrary to the results of the literature our patient presented a pulmonary progression after the use of the CVD protocol.

**Metabolic radiotherapy (table 2)**

MIBG, a guanethidine analog, is selectively concentrated in chromaffin storage granules due to uptake by the same mechanisms responsible for uptake and storage of catecholamine (10). The agent, however, has no affinity for adrenergic receptors.

Malignant pheochromocytoma can be treated with radionucleotides. Van Hulsteijn, reported seventeen studies including 243 patients with paraganglioma / pheochromocytoma malignant treated with 131I-MIBG therapy. He suggested that stable tumor volume and partial hormonal response could be achieved in 50% of cases, if treated with 131I-MIBG. (11-12)

Loh et al. (13) studied 116 patients treated with [131I] MIBG prior to 1997, including 89 patients for whom follow-up data were available. Individual doses generally ranged from 3.7 to 7.4 GBq and were administered repeatedly at intervals of several months. Progression was evident in 13% of cases. Biochemical data were available from 96 individuals who had complete normalization of urinary catecholamines or their metabolites in 13% of cases, partial normalization in 32% and unchanged or increasing values in 55% of cases.

In our case, the radionucleotide treatment is not available.

**Targeted therapy (table 3)**

The mTORinhibitor everolimus in combination with octreotide was evaluated for low and intermediate grade neuroendocrine tumors with good results(14). The efficacy of everolimus was also evaluated in malignant pheochromocytoma, but all patients experienced disease progression (15).

Imatinib, another tyrosine kinase inhibitor already used in hematological and gastrointestinal stromal tumors, has not been shown to be effective in the treatment of malignant CCP [16].

Thalidomide, targeting VEGF has been used in combination with temozolomide in neuroendocrine tumors [9], achieving an objective biochemical response rate of approximately 40% and a radiological response rate of 33% of malignant pheochromocytomas, but lymphopenia has occurred in approximately 70% of patients.

Choung and al reported that seventeen patients with progressive metastatic pheochromocytoma and / or paraganglioma were treated with sunitinib at a dose of 50 mg (four weeks of treatment / two weeks of rest) with a reduction in height tumor, stabilization of the disease and improvement of hypertension in some patients. (17)

**Prognosis**

There are no clear data regarding the survival of patients with regional disease. Although patients with localized (apparently benign) disease should experience an overall survival approaching that of age-matched disease-free individuals, 6.5% to 16.5% of these patients will develop a recurrence, usually 5 to 15 years after initial surgery(18-19)

Approximately 50% of patients with recurrent disease experience distant metastasis. The 5-year survival in the setting of metastatic disease is 40% to 45%. (20)
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Figure 1: local relapse of malignant pheochromocytoma

Figure 2: the onset of pulmonary metastases with stability of the huge mass of local relapse: Failure of chemotherapy
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<table>
<thead>
<tr>
<th>Study</th>
<th>Radiological response</th>
<th>Biochemical response</th>
<th>Reduction of use of antihypertensive</th>
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<tbody>
<tr>
<td>Hamilton BP and al (1): streptozocin, 2pts</td>
<td>Ineffective</td>
<td>Ineffective</td>
<td>-</td>
</tr>
<tr>
<td>Feldman JM and al (2): streptozocin, 1 pts</td>
<td>25% R of adrenal mass 50% R of hepatic metastasis</td>
<td>-</td>
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</tr>
<tr>
<td>Bukowski RM and al (3): streptozocin + cyclophosphamide, 5FU, 2pts</td>
<td>Partial R: 2pts</td>
<td>Biochemical R: 11 pts median duration: 22 months.</td>
<td>-</td>
</tr>
<tr>
<td>Averbuch SD and al (5): CVD, non-randomized study of 14 patients.</td>
<td>Complete R: 2pts  Partial R: 6pts median duration: 21 months.</td>
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<td>-</td>
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<tr>
<td>Srimuninnimit V and al (7): cisplatin and 5-fluorouracil-case report</td>
<td>-</td>
<td>-</td>
<td>1 pts</td>
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<tr>
<td>Nakane M and al: (8): ACVD case report.</td>
<td>-</td>
<td>1 pts</td>
<td>1pts</td>
</tr>
<tr>
<td>Vincitore M and al (9): Temozolomide and Thalidomide: 3 cases of metastatic pheochromocytoma.</td>
<td>Radiological R: 1pts</td>
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**Table 1:** The main publications concerning the different protocols of chemotherapy in malignant pheochromocytoma (pts: patients, R: response).

<table>
<thead>
<tr>
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<th>Biochemical response</th>
<th>Reduction of use of antihypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Hulsteijn and al (12): 243 patients</td>
<td>stable R: 50% partial R: 50%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Loh et al (13): 116 pts (Biochemical data 96 pts)</td>
<td>Progression: 13% complete R: 13% partial R: 32% stable R and progression: 55%</td>
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**Table 2:** The main studies of targeted therapy in malignant pheochromocytoma (pts: patients, RO: objective response).

IV. Conclusion

The malignant pheochromocytoma is a rare tumor. Chemotherapy, metabolic radiotherapy and targeted therapy are the main therapeutic options recommended. In spite of these options, the resistance and the rapid relapse remain rather frequent.

References

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[16]. D. J. Gross, G. Munter, M. Bitan et al., “The role of imatinib mesylate (Glivec) for treatment of patients with malignant endocrine tumors positive for c-kit or PDGF-R,” Endocrine-Related Cancer, vol. 13, no. 2, pp. 535–540, 2006


