TREATMENT FOR METASTATIC NASOPHARYNGEAL CARCINOMA

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Summary
Nasopharyngeal carcinoma (NPC) is a specific entity different from head and neck carcinoma. Incidence is higher in South-East Asia and North Africa. Prognosis, especially for locally advanced stages (IIB - IVB) and metastasis, remains poor: more than third of cases will present local and/or metastatic recurrence. Overall 5-year survival for all NPC stages ranges from 50% to 70%.

The role of chemotherapy in metastasis is well established, and remains an important palliative treatment, although no randomized trial has been reported comparing the different chemotherapy regimens. As 1st-line treatment, platin-based regimens seems optimal; in 2nd line and after progression under platinis, there is no consensus: monotherapy with drugs such as gemcitabine, capecitabine or taxanes has been the most widely tested, with acceptable results. Future trials should integrate targeted therapy, in the light of overexpression of EGFR1 and C-kit in NPC.

The present study presents a review of the literature concerning the various studies of metastatic NPC.

Introduction
Nasopharyngeal carcinoma (NPC), of epidermal origin, constitutes 90% of malignant nasopharyngeal tumors. It is classified in two clinico-histologically distinct entities: epidermoid carcinoma, and undifferentiated carcinoma of nasopharyngeal type (UCNT); the latter shows the greater prevalence worldwide. UCNT differs from other forms of epidermoid carcinoma of the upper aerodigestive tract (UADT) in its histologic features, and an epidemiology unrelated to alcohol or smoking but with a direct relation to Epstein-Barr virus (EBV). It is endemic in certain areas (highly in South-East Asia, and, to a slightly lesser extent, in North Africa) [1], with multifactorial etiology implicating genetic, viral and environmental factors.

Unlike other head and neck tumors, NPC shows a rate as high as one-third for local or locoregional recurrence or metastasis. [2]. The role of chemotherapy is well established for metastasis, with a high level of objective response, enduring remission and some cases of long survival [3].

The present study is an update of recent data regarding the management of metastatic nasopharyngeal carcinoma.
Table 1  Results for monochemotherapy with or without pretreatment.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>n</th>
<th>Molecule</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>med PFS</th>
<th>med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dugan M et al., 1993</td>
<td>Ph II</td>
<td>108 R + M pretreated and not</td>
<td>Mitoxantrone</td>
<td>25</td>
<td>n.r</td>
<td>4.5 months</td>
<td>13 months</td>
</tr>
<tr>
<td>Au E et al., 1998</td>
<td>Ph II</td>
<td>24 M non-treated</td>
<td>Paclitaxel/3 sem</td>
<td>21.7</td>
<td>0</td>
<td>7.5 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Poon D et al., 2005</td>
<td>Ph II</td>
<td>28 M pretreated</td>
<td>Irinotecan</td>
<td>14</td>
<td>0</td>
<td>3.9 months</td>
<td>11.4 months</td>
</tr>
<tr>
<td>Foo KF et al., 2002</td>
<td>Ph II</td>
<td>25 M pretreated</td>
<td>Gemcitabine</td>
<td>28</td>
<td>4</td>
<td>3.6 months</td>
<td>7.2 months</td>
</tr>
<tr>
<td>Zhang L et al., 2008</td>
<td>Ph II</td>
<td>32 pretreated</td>
<td>Gemcitabine</td>
<td>43.8</td>
<td>0</td>
<td>5.1 months</td>
<td>16 months</td>
</tr>
<tr>
<td>Ph II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63% (1 year)</td>
<td>6% (1 year)</td>
</tr>
<tr>
<td>Ph II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54% (1 year)</td>
<td>62% (1 year)</td>
</tr>
<tr>
<td>Ph II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% (1 year)</td>
<td>14 months</td>
</tr>
<tr>
<td>Ph II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14 months</td>
<td>62% (1 year)</td>
</tr>
<tr>
<td>Ph II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3 months</td>
<td>12.8 months</td>
</tr>
</tbody>
</table>

OR: Objective response; CR: Complete response; n: Number of patients; med PFS: Median progression-free survival; med OS: median overall survival; n.r: not recorded; Ph II: Phase II; Retro: Retrospective; M: Metastatic; R: Recurrent.

Methodology

The Medline database was searched for the period 1980 to end 2009, using the keywords “nasopharyngeal carcinoma”, “metastatic”, “chemotherapy” and “targeted therapy”.

Diagnosis of metastasis

Extension assessment

Treatment strategy varies depending on whether recurrence is local or metastatic, thus requiring thorough assessment of remote extension, comprising lung X-ray and abdominal ultrasound scan or thoraco-abdominal CT scan, associating, particularly in case of stage N+ and above all N3 lymph-node involvement, bone scintigraphy.

Positron emission tomography (PET scan) detects metastatic locations (lymph-node or other remote metastases) with good sensitivity and may influence treatment strategy [4], although comparative studies are needed to validate this promising attitude.

Metastasis epidemiology

Remote metastasis is frequent in NPC, with very high rates on autopsy series, varying between 38 and 87% [5]; on initial diagnosis, metastasis is found in just 5 to 7% of patients [6]. These are mainly metachronous metastases discovered in the course of evolution, usually within 3 years of treatment. The overall rate of metastasis is 25–30%;[6].

The occurrence of metastasis is related to tumor size (T) and especially to lymph-node involvement (N), and is most frequent in T3-4 or N2-3 tumor and in patients presenting with the UCNT histologic type [7].

The most frequent metastasis location is the bone (70–80%), followed by viscera (liver, 30%; lung, 18%) and, at lower rates, extra-cervical lymph-nodes (axillary, mediastinal, pelvic, inguinal) [8].

Prognosis depends on location: hepatic and/or medullary involvement is of poor prognosis, while isolated bone metastasis may be associated with long survival [9].

Medical management of metastatic NPC

Chemotherapy

Chemotherapy is the basic treatment for metastatic NPC, with numerous published confirmations of efficacy. Median survival, however, is short.

It is a remarkable fact that no randomized studies have compared palliative chemotherapy versus other palliative care, or different chemotherapy protocols. Quality of life has been little investigated. Studies have all been retrospective or phase II;

Studies of chemotherapy in metastatic NPC are difficult to compare, with small non-randomized series, and no particular protocol can thus be demonstrated to be preferentially effective;
Table 2  Results for bitherapy in local recurrence and/or metastasis with or without pretreatment.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>n</th>
<th>Protocol</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>med PFS</th>
<th>med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang T.L. et al., 1991 [22]</td>
<td>Retro</td>
<td>25 M</td>
<td>Cisp + 5FU</td>
<td>76</td>
<td>8</td>
<td>n.r</td>
<td>n.r</td>
</tr>
<tr>
<td>Au E. et al., 1994 [23]</td>
<td>Ph II</td>
<td>24 R + M</td>
<td>Cisp + 5FU</td>
<td>66</td>
<td>13</td>
<td>8 months</td>
<td>11 months</td>
</tr>
<tr>
<td>Chi KH et al., 1994 [24]</td>
<td>Ph II</td>
<td>20 R</td>
<td>15 M</td>
<td>Cisp + 5FU/Lv</td>
<td>1080</td>
<td>15 13</td>
<td>n.r</td>
</tr>
<tr>
<td>Stein ME et al., 1996 [25]</td>
<td>Ph II</td>
<td>18 R + M</td>
<td>Cisp + Ifos</td>
<td>59</td>
<td>15</td>
<td>n.r</td>
<td>n.r</td>
</tr>
<tr>
<td>[5pt] Yeo W et al., 1996 [26]</td>
<td>Ph II</td>
<td>42 M</td>
<td>Carbo + 5Fu</td>
<td>38</td>
<td>17</td>
<td>n.r</td>
<td>12.1 months</td>
</tr>
<tr>
<td>Yeo W et al., 1998 [27]</td>
<td>Ph II</td>
<td>27 R + M</td>
<td>Carbo + Pac</td>
<td>59</td>
<td>11</td>
<td>6 months</td>
<td>13.9 months</td>
</tr>
<tr>
<td>Tan EH et al., 1999 [28]</td>
<td>Ph II</td>
<td>32 M</td>
<td>Carbo + Pac</td>
<td>75</td>
<td>3</td>
<td>7 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Ciuleanu TE et al., 2004 [29]</td>
<td>Ph II</td>
<td>40 M</td>
<td>Carbo + Pac</td>
<td>27.5</td>
<td>7.5</td>
<td>3.5 months</td>
<td>11.5 months</td>
</tr>
<tr>
<td>Ngan RK et al., 2002 [30]</td>
<td>Ph II</td>
<td>44 R + M</td>
<td>Cisp + Gem</td>
<td>73</td>
<td>20</td>
<td>10.6 months</td>
<td>15 months</td>
</tr>
<tr>
<td>Ma BB et al., 2002 [16]</td>
<td>Ph II</td>
<td>14 R + M</td>
<td>Cisp + Gem</td>
<td>64</td>
<td>14</td>
<td>13% (1 year)</td>
<td>68% (1 year)</td>
</tr>
<tr>
<td>Wang J et al., 2008 [31]</td>
<td>Retro</td>
<td>75 R + M</td>
<td>Cisp + Gem</td>
<td>42.7</td>
<td>5.3</td>
<td>5.6 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Ma BB et al., 2009 [32]</td>
<td>Ph II</td>
<td>40 R + M</td>
<td>Oxali + Gem</td>
<td>56.1</td>
<td>0</td>
<td>9 months</td>
<td>19.6 months</td>
</tr>
<tr>
<td>McCarthy et al., 2002 [33]</td>
<td>Ph II</td>
<td>9 R + M (1st l)</td>
<td>Cisp + Doc</td>
<td>22</td>
<td>0</td>
<td>8.4 months</td>
<td>76% (1 year)</td>
</tr>
<tr>
<td>Chua.DT et al., 2005 [34]</td>
<td>Ph II</td>
<td>19 M (1st l)</td>
<td>Cisp + Doc</td>
<td>62.5</td>
<td>6.3</td>
<td>5.6 months</td>
<td>12.4</td>
</tr>
<tr>
<td>Li YH et al., 2008 [35]</td>
<td>Ph II</td>
<td>48 M (1st l)</td>
<td>Cisp + Cape</td>
<td>62.5</td>
<td>6.3</td>
<td>7.7 months</td>
<td>13.3 months</td>
</tr>
<tr>
<td>Chua DT et al., 2000 [36]</td>
<td>Ph II</td>
<td>18 R + M</td>
<td>Ifos + 5FU/Lv</td>
<td>56</td>
<td>6</td>
<td>6.5 months</td>
<td>51% (1 year)</td>
</tr>
<tr>
<td>Huang HQ et al., 2002 [37]</td>
<td>Ph II</td>
<td>34 R + M</td>
<td>Ifos + Doc</td>
<td>67.6</td>
<td>14.7</td>
<td>6 months</td>
<td>n.r</td>
</tr>
<tr>
<td>Altundag K et al., 2004 [38]</td>
<td>Ph II</td>
<td>21 R + M</td>
<td>Ifos + Doc</td>
<td>33.3</td>
<td>0</td>
<td>7 months</td>
<td>n.r</td>
</tr>
<tr>
<td>Wang CC et al., 2006 [39]</td>
<td>Ph II</td>
<td>39 M (2nd–3rd l)</td>
<td>Gem + VNR</td>
<td>36</td>
<td>3</td>
<td>5.6 months</td>
<td>11.9 months</td>
</tr>
</tbody>
</table>

Monochemotherapy

The chemotherapy agents most often used in monotherapy in older reports were methotrexate, bleomycin, 5-fluoro-uracile (5FU), cisplatin and carboplatin, with response rates in the region of 15 to 31% [10]. Two phase II trials specifically focusing on metastatic nasopharyngeal cancer reported two other drugs as showing efficacy: an anthracycline (4-epidoxorubicine) and mitoxantrone, with objective response (OR) rates of about 20% [11,12].

More recent clinical trials tested other molecules (gemcitabine, capecitabine, paclitaxel, docetaxel and irinotecan) in monotherapy in patients pretreated with cisplatin [13–21] (Table 1); two (gemcitabine and capecitabine) have been the focus of several reports, with interesting OR rates in the range of 23–48% and median survival of between 7.2 and 14 months [15–20]; more recently again, the first study of docetaxel in monotherapy in this indication reported comparable results [21].

Polychemotherapy

First-line polychemotherapy with platin-based doublets [22–30,16,31–35] gave interesting response rates: OR, 50–90%; complete remission (CR), 5–30% (Table 2). These rates were higher than obtained with isolated cisplatin. In second line following platin resistance, associations without platin have been tested, but not subjected to randomized assessment [36–39].

The association of cisplatin (100 mg/m²) and 5FU in continuous perfusion (1 g/m²) for 3–5 days was the most frequently tested polychemotherapy protocol in the older studies, giving OR between 66% and 78% and median survival up to 11 to 14 months [22–24]; by virtue of its activity, low myelotoxicity and good tolerance, this association is the standard first-line attitude in several centers in Asia.

In recent studies, platin (cisplatin, carboplatin or oxaliplatin) were associated with other molecules: gemcitabine, paclitaxel, docetaxel or capecitabine [27–30,16,31–35]; paclitaxel-carboplatin [27–30], gemcitabine-cisplatin [30,16,31] and docetaxel-cisplatin [33,34] were the most widely tested, giving similar results: OR 25–75% and median survival 9.5–15 months. There has, however, been no randomized comparison against 5FU-cisplatin.

Other studies tested polychemotherapy protocols associating platin and more than two other drugs, but without finding any major impact on survival (Table 3). The CAPABLE trial, for example, associated five molecules (cisplatin, methotrexate, bleomycin, cyclophosphamide and adriamycin) and obtained a very good OR rate of 80% with 7% CR, but at the cost of very elevated toxicity and a high rate of iatrogenic death (11%) with no improvement in overall survival (OS) [40]. Other trials reported similar findings: improved OR but elevated toxicity inducing 11–13% mortality with no benefit in terms of OS [40–47].
Table 3: Results for polychemotherapy (> 2 molecules) in local recurrence and/or metastasis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>n</th>
<th>Protocol</th>
<th>OR (%)</th>
<th>CR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boussen H., et al 1991</td>
<td>Ph II</td>
<td>49</td>
<td>Cisp + B + 5FU</td>
<td>79</td>
<td>19</td>
<td>9.5%</td>
<td>n.r</td>
<td>Neutropenia Gr 3/4: 36%) Toxic death: 12%</td>
</tr>
<tr>
<td>Su W., et al 1993</td>
<td>Ph II</td>
<td>25</td>
<td>Cisp + B + 5FU</td>
<td>40</td>
<td>3</td>
<td>n.r</td>
<td>n.r</td>
<td>Neutropenia Gr 3/4: 36%) Toxic death: 12%</td>
</tr>
<tr>
<td>Azli N., et al 1995</td>
<td>Ph II</td>
<td>44</td>
<td>BEC B + Epi + Cisp</td>
<td>45</td>
<td>20</td>
<td>8.9% (53</td>
<td>n.r</td>
<td>Neutropenia Gr 3/4: 36%) Toxic death: 12%</td>
</tr>
<tr>
<td>Siu LL., et al 1998</td>
<td>Ph I/II</td>
<td>17 R</td>
<td>CAPABLE</td>
<td>41</td>
<td>23.5</td>
<td>6.8</td>
<td>n.r</td>
<td>Toxic death 11.5%</td>
</tr>
<tr>
<td>Taamma A., et al 1999</td>
<td>Ph II</td>
<td>23</td>
<td>FBEC 5FU + B + Epi + Cisp</td>
<td>78</td>
<td>39</td>
<td>13% (42</td>
<td>n.r</td>
<td>Neutropenia Gr 3/4: 36%) Toxic death: 13%</td>
</tr>
<tr>
<td>Hasbini A., et al 1999</td>
<td>Ph II</td>
<td>44</td>
<td>FMEP 5FU + M + Epi + Cisp</td>
<td>52</td>
<td>13</td>
<td>9 months</td>
<td>14 months</td>
<td>Neutropenia Gr 3—4: 89% Febrile neutropenia: 36% Mucitits Gr 3—4 32% Toxic death (9%)</td>
</tr>
<tr>
<td>Leong SS., et al 2008</td>
<td>Ph II</td>
<td>28</td>
<td>Carbo + G + Pacli + 5FU/Lv (maint)</td>
<td>86</td>
<td>11</td>
<td>8 months</td>
<td>22 months</td>
<td>Neutropenia Gr 3/4: 79% Anemia Gr 3—4: 32%</td>
</tr>
<tr>
<td>Huang HQ., et al 2008</td>
<td>Ph II</td>
<td>56</td>
<td>DCF (Doc + Cisp + 5FU)</td>
<td>72.5</td>
<td>9.8</td>
<td>n.r</td>
<td>n.r</td>
<td>Neutropenia Gr 2—4: 10.5% Febrile neutropenia: 3.6%</td>
</tr>
</tbody>
</table>

OR: Objective response; CR: Complete response; med PFS: Median progression-free survival; med OS: median overall survival; n: Number of patients; n.r: not recorded; M: Metastatic; R: Recurrent; Ph II: Phase II; Retro: Retrospective; Cisp: Cisplatin; 5FU: 5-Fluorouracil; Ifos: Ifosfamide; Pac: Paclitaxel; Doc: Docetaxel; G: Gemcitabine; Carbo: Carboplatin; B: Bleomycine; Cape: Capecitabine; Oxali: Oxaliplatin; VNR: Vinorelbine; LV: Leucovorin; CAPABLE: Cyclophosphamide + Bleomycin + Doxorubicin + Cisplatin; DCF: Docetaxel + 5FU + Cisplatin; Maint: Maintenance; Gr: Grade.

The results of the published trials are to be interpreted with caution before considering one protocol or drug as more effective than another: the studies are very divergent, with heterogeneous populations, including isolated locoregional recurrence or metastasis, with and without pretreatment, first, second and third line treatments, having already received platins or not; they were moreover mainly retrospective studies or phase II trials and not randomized.

Choice of first and second line chemotherapy
In first-line treatment of metastasis, platin-based bitherapy is generally recommended, and 5FU cisplatin in particular [48].

In second line treatment of metastasis, the choice of chemotherapy depends on the previous treatment. In patients pretreated with platins, there is no established standard, reintroduction of platins depending on toxicity and the interval to recurrence: for an interval greater than
6–12 months, a second platin-based doublet associating taxanes or gemcitabine seems to be the most effective, with OR 22–75% but with associated grade 3–4 hematologic toxicity, which my act as a limitation. Second line capecitabine, gemcitabine or docetaxel monochemotherapy is recommended in case of platin resistance (early [< 6 months] recurrence) or in fragile subjects in whom toxicity could be threatening [48].

**Targeted therapy**

There are few studies of targeted treatment of metastasis, but Phase II studies have been published in the light of overexpression of EGFR1 and C-kit. Gefitinib was tested in two studies; results were disappointing, with no OR but rather stabilization: a first phase II study on a small series of 19 patients with local recurrence or metastasis after second line failure of chemotherapy reported no OR, 4 months’ progression-free survival (PFS) and 16 months’ OS [49]; the second study, which was stopped for lack of efficacy, concerned 15 patients, showing 20% stabilization, 2.7 months’ PFS and 12 months’ OS [50].

Another tyrosine kinase inhibitor (TKI), sorafenib, was tested in epidermoid head and neck carcinoma and metastatic or recurrent NPC after at least one line of chemotherapy, but showed weaker response than found for chemotherapy [51].

A phase II study tested a monoclonal antibody, cetuximab, in association with carboplatin in 59 patients overexpressing EGFR, in local or metastatic recurrence 12 months after platin chemotherapy: again, response was weak, often with stabilization (OR 11.7%, CR 0%, disease stabilization 48.3%), at the cost of significant toxicity (grade 3/4: 51.7%), median PFS being 2.8 months and OS 7.8 months after platin chemotherapy [52].

**Other treatments for metastasis**

**Locoregional radiation therapy**

In primary metastasis, locoregional radiation treatment may be indicated after control by chemotherapy; it improves disease control and quality of life [53].

**Metastasis surgery**

Pulmonary metastasis resection may be recommended for limited pulmonary metastasis; good resultant control was reported [54].

**Role of bisphosphonates**

Recent studies demonstrated specific efficacy of bisphosphonates in bone metastases of NPC [55].

**Conclusion**

In metastasis, chemotherapy is mandatory for patients with a good performance status index; the 5FU-cisplatin association is most widely used in first-line; recent studies showed other drugs to be effective, in monotherapy or in association: docetaxel, paclitaxel, gemcitabine and capecitabine.

However, well-designed randomized studies will be needed, in order to determine treatment standards. Moreover, targeted therapy should be included in future trials.

**Conflict of interest statement**

None.

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Treatment for metastatic nasopharyngeal carcinoma

