IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 8 Ser.4 (August. 2023), PP 29-33
www.iosrjournals.org

Induction Chemotherapy With TPF Plus Radiochemotherapy In Undifferentiated Carcinoma Of The Nasopharyngeal Type (UCNT)

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Abstract
We represent in this study the long term results of docetaxel, cisplatin and 5-fluorouracil chemo-induction followed by concurrent chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma type Undifferentiated Carcinoma of the Nasopharyngeal Type (UCNT). The primary endpoint was overall response rate (ORR) after induction CT and after cCTRT. Secondary end points were safety, disease free survival (DFS), and overall survival (OS).

Patients and methods
Between December 2007 to December 2012, 42 patients with locoregional advanced diseasewere treated in our institution by three cycles of docetaxel, cisplatin and 5-fluorouracil induction chemotherapy every every 4 weeks with G-CSF days 1-5, followed by concurrent chemoradiotherapy. Conventional radiotherapy was delivered during 7 weeks with weekly cisplatin (40mg/m^2).

Results
42 pts have been enrolled (26 M/16 F). UICC 1997 classification: n=9 stage II, n=10 stage III, n=23 stage IV. Median age is 37 yrs (range 18-64). Evocative clinical signs are cervical nodes n=20, rhinologic n=13, otologic n=5, and neurologic n=4. All pts were evaluated for safety and 38 for response.TPF well tolerated with main toxicities grade 3-4 (WHO) were neutropenia 36%, thrombocytopenia 32%, anemia 18%, diarrhea 6%, and mucositis 18%. Four pt died from sepsis that was probably treatment related. ORR was 90% with an 71.4% (n=27) complete response (CR) rate, 23.6% (n=9) partial response (PR), and 5.2% (n=2) stable disease. No pts progressed after induction CT. Main toxicity during cCTRT was neutropenia grade 3-4 in 9%, mucositis grade 3 in 45% and grade 4 in 4%. Late toxicities were xerostomia grade 3 in 50%. At treatment completion, CR and PR rates were 79% and 20%; 2 pts had stable disease. At a median follow up of 72 months (range 7-72), 8% of pts have shown recurrence or progressive disease. DFS and OS rates at 72 months were 65% and 70%, respectively.

Conclusion
The results of our series show that TPF-type induction chemotherapy in locally advanced UCNT deserves to be analyzed in larger cohorts; for the positive impact on recurrence-free survival, distant metastasis-free survival and overall survival and on the toxicity profile almost similar to the PF protocol.

Keys words *: UCNT, Induction chemotherapy, chemoradiotherapy*

Date of Submission: 04-08-2023 Date of Acceptance: 14-08-2023

I. Introduction:

The UCNT (undifferentiated carcinoma of nasopharyngeal) is a malignant epithelial tumor that most commonly develops in the fossa of Rosenmüller . Due to its anatomic location and non-specific symptoms, 80% of patients present with advanced locoregional disease at the time of diagnosis [1].Characterized by a particular geographical distribution, more than 130,000 patients were recorded worldwide in 2020, with the highest rates being observed in the regions of China,

Southeast Asia and North Africa[2]. Gold standard in the therapeutic management of UCNT,Concomitant radio-chemotherapy (CCR) has forged its results on the very properties of the pathology, which are chemo-sensitivity and radio-curability [3,4,5]. However, more than 25% of patients will suffer from

distant metastases despite a well-conducted treatment based on RCC [6]. Thus, the rationale for a more effective treatment strategy was born based on induction chemotherapy.

Several large-scale clinical studies have demonstrated that the use of chemo-induction prior to CCR can significantly improve overall survival, progression-free survival, and distant metastasis-free survival in the treatment of patients with UCNT locally advanced [7–11]. Based on these encouraging results, chemo-induction followed by CCR might be a promising treatment strategy [12,13]. However, the optimal chemo-induction regimen has not been established, as no large-scale comparative studies have been performed.

Initially, the cisplatin-fluorouracil (PF)-based chemo-induction regimen was considered the preferred choice in the treatment of head and neck cancers [7,14]. Since then, several phase 3 trials have confirmed statistically significant survival benefits of adding docetaxel to a PF-based chemo-induction regimen and defined TPF as the optimal regimen for head cancers. and neck [15,16]. However, UCNT differs from other head and neck cancers in terms of its etiology, pathology, epidemiology, clinical presentation, and responses to treatment [3]. Currently, whether TPF is an ideal chemoinduction regimen remains controversial in the management of UCNT.

II. Materials and method:

The prospective cohort study was conducted over a period of 72 months from December 2007 to December 2012, at the medical oncology department of the Pierre and Marie Curie Center in Algiers. All patients underwent a clinical examination (complete ENT examination and nasofibroscopy) and an initial assessment including radiological assessment (scan of the cavum, magnetic resonance imaging of the cavum, abdominal CT scan and bone scintigraphy) and biological assessment. At the end of this assessment, the pathology was classified according to the TNM 2009 classification of the UICC (International Union Against Cancer).

Patients treated with induction chemotherapy followed by concomitant radio-chemotherapy had to meet the following inclusion criteria:

- Patients with locally advanced UCNT
- Diagnosis based on histology
- No previous chemotherapy
- ECOG Performance Status (PS)≤02
- Correct renal and hepatic function
- Informed consent

Chemo-induction was performed according to the following scheme: 3 cycles of TPF (docetaxel 75 mg/m2 and cisplatin 75/m2 day 1, plus fluorouracil 750 mg/m2 days 1-5, every 4 weeks with G-CSF days 1-5, followed by CCR with cisplatin 40 mg/m2/week and radiotherapy (65-70 Gy) started 4 to 6 weeks after the 3rd cycle of chemo-induction.

The data is collected on standardized forms in the form of a questionnaire and then analyzed on software such as spss 20.00, in univariate analysis. The descriptive analysis of the variables was made by calculating the frequencies and confidence intervals for the qualitative variables, the central tendency or the characteristics of dispersion: the mean (m), the median (me), as well as the determination of the confidence interval (95% CI) around the mean and the median (me) for the quantitative variable.

During the inclusion period from December 2007 to December 31, 2012, 200 Patients with UCNT were collected at the Medical Oncology department of CPMC Algiers at all stages. 42 patients were admitted to our study, meeting the inclusion criteria. Our study population is composed of 16 women (%) and 26 men (%), ie a sex ratio of 1.62.

The average age at diagnosis of patients is 37 years with extremes ranging from 18 to 64 years, an interval of 46 years. The median age of the study population is 41 years. Note that the curve according to the age groups is unimodal, with a frequency peak in the 41-45 age group, which represents 1/3 of our study population.

The clinical signs found are, in the majority of cases, indicative of the advanced stage of the disease. They are often associated, rarely isolated. Cervical lymphadenopathy was found in 20 patients (47.6%); rhinological syndrome (nasal obstruction and/or epistaxis) was found in 13 (31%) patients, otological syndrome was present in 6 (14.3%) patients in our series, and neurological syndrome in 7 (16.7%) %) patients.

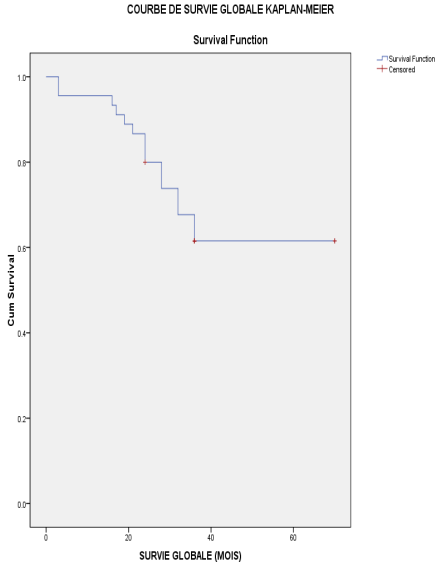
Chemo-induction was performed in 33 (78.5%) patients, and 9 (21.5%) of the patients received concomitant radiochemotherapy alone. The average time between the end of chemo-induction and the start of radiotherapy was 6 weeks . After a mean follow-up of 72 months, calculated from the end of treatment date, overall survival was 70% (f and recurrence-free survival 65%. None of our patients had a recurrence among patients with stage II disease during this period. Analysis of

recurrence-free survival according to the various prognostic factors showed a statistically significant difference for lymph node invasion with rates RFS at three years of 88%, 82.6%, 80.8% and 61.5% respectively in the case of N0, N1, N2 and N3 tumors ($p = 0.02$).

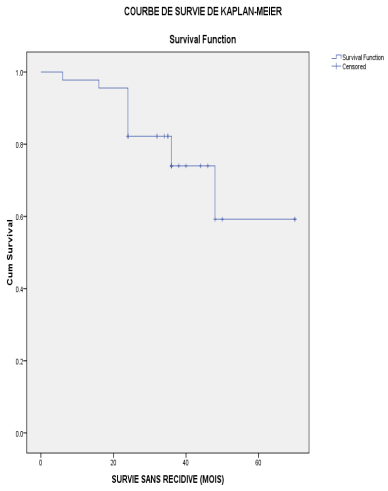
For the other prognostic factors studied, the difference was not statistically significant.
All patients were evaluated for toxicity. TPF was well tolerated and the main grade 3-4 toxicities (WHO) were:

- neutropenia 36%
- thrombocytopenia 32%
- anemia 18%,
- diarrhea 6%
- mucositis 18%.

It should be noted that four (04) patients died of sepsis on febrile neutropenia probably related to the treatment.



OS= 52.3 months (43-60) IC 95%



DFS = 55.19 months (47-63) IC 95%

III. Discussion :

Meta-analyses have demonstrated an overall survival benefit of adding concurrent chemotherapy to radiotherapy in patients with locally advanced UCNT [7]. Despite well-conducted RCC-based treatment, metastatic recurrences affect more than 30% of patients with locally advanced UCNT, leading in the majority of cases to death [6,17]. The use of induction chemotherapy in case of locally advanced UCNT has given better results, on the one hand, in the control and eradication of the micro-metastatic disease, and local recurrences on the other.

For chemo-induction, the PF protocol is most commonly used. A first randomized study was conducted to compare two cycles of chemo-induction based on FP followed by radiotherapy versus

radiotherapy alone. The 5-year distant metastasis-free survival for patients in the chemo-induction + radiotherapy arm was 74% versus 56% for patients in the radiotherapy alone arm. [18]

TAX 323 was the first study to demonstrate the benefits of adding Docetaxel to Cisplatin and 5-Fluorouracil as induction chemotherapy for locoregionally advanced head and neck cancer. Patients in the TPF group experienced a significant 27% reduction in mortality and an improvement in median OS of 4.3 months [19].

Additionally, Sun et al conducted a randomized phase III study to compare three cycles of continuous intravenous Docetaxel, Cisplatin, and Fluorouracil induction followed by RCC versus RCC alone. [9] Induction chemotherapy significantly increased the rates of 3-year failure-free survival, overall survival, and distant metastasis-free survival in their patient population. More recently, a phase III multicenter randomized controlled trial reported that IC improved 3-year disease-free survival (P=0.028) and distant metastasis-free survival rates (P=0.056) compared to DCR alone in locally advanced UCNT [8].

It can also be noted that the TAX 324 study andGORTEC laryngeal studyshowed that TPF was significantly better than PF in improving survival, local control, and organ preservation and was associated with manageable toxicity [15,20,21].

A retrospective study published in 2018 byGuo-Ying Liu et al demonstrated the interest of using chemo-induction based on a TPF regimen in locally advanced UCNT, with better results in recurrence-free survival, distant metastasis-free survival and overall survival. [22].

Another meta-analysis conducted by ZHOU et al and published in 2019 on The efficacy and safety of induction chemotherapy based on docetaxel, cisplatin and fluorouracil (TPF) followed by concomitant chemoradiotherapy for the locally advanced nasopharyngeal carcinoma to further highlight the superiority of the TPF versus PF chemo-induction regimen with a manageable toxicity profile.[23]

In our series, the evaluation of the response after TPF chemotherapy was mainly based on the clinical examination of the cervical lymphadenopathy. The complete response rate was 71.4% and slightly higher than the rates reported in the literature (9% to 26.6%) [10,11].

Regarding acute toxicity during induction chemotherapy, we note in our study a high rate of neutropenia, which can be explained by the lack of systematic use of GCSF and prophylaxis. However, there were no cases of nephrotoxicity or cardiotoxicity. Non-haematological toxicity was dominated by vomiting, asthenia and diarrhea, which is largely consistent with the literature[15, 20, 21, 22,23].The 5-year overall survival and disease-free survival rates were 70% and 65%, respectively.

IV. Conclusion :

Despite the demonstrated interesting results of the addition of chemo-induction to CCR for the treatment of locally advanced UCNT, studies comparing different chemo-induction regimens are rare.The results of our series show that TPF-type induction chemotherapy in locally advanced UCNT deserves to be analyzed in larger cohorts; for the positive impact on recurrence-free survival, distant metastasis-free survival and overall survival and on the toxicity profile almost similar to the PF protocol.

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