REVIEW

Cetuximab-Taxanes-Platinum-Fluorouracil/ Capecitabine (C-TPF/C-TPX) – a Feasible Option for Recurrent HNSCC with Negative Prognostic Factors. Literature Review with a Case Presentation

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Abstract

Concurrent chemo-radiotherapy with Cisplatin is the standard treatment for locally advanced non-metastatic squamous cell carcinoma of the head and neck (HNSCC), but induction chemotherapy (IC) followed by chemo-irradiation, even controversial is a widely accepted option, especially in high- risk cases. A regimen including triple association (platinum-taxanes-fluorouracil) is generally considered superior in efficacy, but may be associated with severe toxicity. In the case of recurrence, the options are limited and the prognosis is generally unfavorable. Chemotherapy alone or in combination with an anti-EGFR monoclonal antibody (Cetuximab), immunotherapy or re-irradiation for selected cases are feasible options in loco-regional or metastatic repalapse. We present a case of nasopharyngeal cancer (NPC), with negative prognostic and predictive factors multimodally treated with an intensive chemotherapy regimen associating Cetuximab with a median survival higher than the median value reported in most studies. Replacing 5-Floururacil with Capecitabine and Cisplatin with Carboplatin may be an option to increase treatment tolerance and should be evaluated in randomized trials. The use of induction chemotherapy as a "new standard" before radio-chemotherapy for cases with negative prognostic factors should also be the subject of future studies. Re-challenge with platinum is also an option that needs to be re-evaluated..

Keywords: chemo-radiotherapy, NPC, TPF, chemotherapy, Cetuximab, Carboplatin, Capecitabine

Rezumat

Chimio-radioterapia concomitentă cu Cisplatină este tratamentul standard pentru carcinomul cu celule scuamoase al capului și gâtului (HNSCC), în standiul local avansat, non-metastatic. Chimioterapia de inducție (IC) urmată de chimio-radioterapie, chiar dacă este o abordare controversată, este o opțiune acceptată la scara largă, mai ales în cazurile cu risc ridicat de metastazare la distanță. Un regim de poli-chimioterapie care include tripla asociere (platină-taxani-fluorouracil) este în general considerat superior ca eficacitate, dar poate fi asociat cu toxicitate severă. În cazul recurenței bolii, opțiunile sunt limitate și prognosticul este adesea nefavorabil. Chimioterapia, ca terapie unica sau în asociere cu un anticorp monoclonal anti-EGFR (Cetuximab), imunoterapia sau re-iradierea pentru cazuri selectate sunt opțiuni fezabile în abordarea recidivei loco-regionale sau a bolii metastatice. Prezentăm un caz de neoplasm nazofaringian (NPC), cu factori prognostici și predictivi negative, tratat intensiv multimodal cu chimioterapie si Cetuximab, supraviețuirea mediană fiind peste valoarea mediană raportată în majoritatea studiilor clinice. Înlocuirea 5-Floruracil cu Capecitabină și a Cisplatin cu Carboplatin pot fi o opțiuni alese pentru creșterea toleranței la tratament și ar trebui evaluate în studii randomizate. Utilizarea chimioterapiei de inducție ca „nou standard" înainte de radio-chimioterapie pentru cazurile cu factori de prognostic negativ ar trebui, de asemenea, să facă obiectul unor studii viitoare. Reinițierea unui tratament pe bază de săruri de platină este, de asemenea, o opțiune care trebuie luată în calcul.

Cuvinte cheie: chimioradioterapie, NPC, TPF, chimioterapie, Cetuximab, Carboplatin, Capecitabine

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INTRODUCTION

Concurrent chemo-radiotherapy with Cisplatin is the standard treatment for locally advanced non-metastatic squamous cell carcinoma of the head and neck (HNSCC). Induction chemotherapy (IC) followed by chemo-irradiation is a controversial and widely accepted option, especially in high-risk cases, with the protocol including a triple association (platinum-taxanes-flourouracil) being generally considered superior in efficacy. In the case of recurrence, the options are limited and the prognosis is generally unfavorable. Chemotherapy alone or in combination with an anti-EGFR monoclonal antibody (Cetuximab), immunotherapy or selective re-irradiation are feasible options in recurrent loco-regional or metastatic disease[1-3].

CASE REPORT

We present the case of a 66 years old patient without significant diseases history excepting a solid latero-cervical solid mass diagnosed 3 years ago and subsequently evaluated by fine needle aspiration (FNA). The pathological examination did not reveal any elements of malignancy. The patient presented in April 2016 to the ENT department of Craiova County University Hospital with solid masses, located latero-cervically on both sides of the neck, larger on the left side. Bilateral neck dissection is performed and pathological examination reveals metastasis of poorly differential squamous cell carcinoma with extensive regions of necrosis and cystic transformation, with Extra-capsular growth (ECG) and invasion of the adjacent tissue. Naso-pharynx biopsy reveals undifferentiated, ulcerated, invasive carcinoma, associated with moderate inflammation. The patient is subsequently evaluated by a multidisciplinary team and considering the waiting lists for radiotherapy, poly-chemotherapy is initiated.

The first sequence of poly-chemotherapy (Docetaxel, Carboplatin plus Capecitabine) was followed by 3D-conformal external beam radiotherapy in a total dose (DT) of 74Gy/35fractions on naso-pharynx and 50Gy/25fractions on cervical limph nodes. 2 more cycles of chemotherapy Docetaxel-Carboplatin-Capecitabine was continued after 3 weeks then radiotherapy was completed (June 2016). After 2 months patient return with dysphonia, right nasal obstruction, rhinorrhea (August 2016). Computer tomography (CT) and ENT including trans-nasal endoscopy highlighted disease progression. ENT endoscopy revealed a solid mass in the middle of the right meat, and the CT imaging exam revealed the deformation of the left naso-pahrynx wall and the diffuse osteolysis of the basilar process. The chest CT examination revealed bilateral apical tuberculosis sequels. After 3rd sequence of poly-chemotherapy-TPF (Taxanes-Platinum-5Fluorouracil) regimen the patient presented severe asthenia odynophagia and nycturia. The next two chemotherapy cycles included a platinum doublet (Docetaxel-Carboplatin). We mention that the substitution of 5fluorouracil with Capecitabine was caused by the unavailability of the drug in pharmacies at that time. Subsequently, the clinical examination in the ENT department and CT evaluation revealed no disease progression. Immuno-hostochemistry (IHC) of the primary tumor sample was performed, with negatives VEGF and ALK, EGFR and positives Ki67 and P53. Biological therapy with Cetuximab was initiated 10 months from the diagnosis (January 2017). CT evaluation 6 months after initiation of biological therapy revealed bilateral maxillary sinusitis and an inhomogeneous tumor mass, intensely iodophilic of 4.7 / 3.2 cm, on the right lateral wall of the naso-pharynx with extension in the right maxillary sinus and right nasal fossa and to right ethmoid cells. Endoscopic evaluation in the ENT department revealed tumor mass in the middle and upper right meatus, tumor biopsy being performed. After the pathological confirmation of disease recurrence, a rechallenge of platinum base chemotherapy was proposed with Carboplatin-5Fluorouracil regimen in association with biologic therapy with Cetuximab. The case was proposed for re-evaluation for re-irradiation option, being considered outside the therapeutic resources considering the risks higher than the benefits. CT imaging follow-up at 8 months (September 2017) from the initiation of biological therapy revealed bilateral sphenoid and ethmoidal sinusitis, a tumor mass in both nasal fossae associating osteolysis of sphenoid and ethmoidal sinuses walls bilaterally, of the median wall of right maxillary sinus, clivus and also of tumor adjacent bone structures. Right jugulo-carotid lymphadenopathy, bilateral submandibular and left submental lymphadenopathy were also identified. In November 2017, being considered tumor progression, the poly-chemotherapy with TPF protocol was restarted in association with Cetuximab biotherapy. From November 2017 to February 2018, the 6th-8th TPF chemotherapy cycles were administered. In February

2018 patient presented severe asthenia and skin rash. It is decided to initiate 2nd line chemotherapy in the Gemcitabine-Carboplatin regimen. Until November 2018, 5 cycles of Gemcitabine-Caboplatin polychemotherapy are administered, during the treatment the patient presenting grade 2 leukopenia and anterior epistaxis, odynophagia and fatigue. In December 2018, the patient refused the proposed mono-chemotherapy with Carboplatin, requiring supportive treatment, anticoagulant and nasal tamponade for recurrent bleedings. The patient dies 10 months after stopping active cancer treatment (September 2019).

In summary, the case highlights the option of aggressive management by poly-chemotherapy (8 TPF cycles of which in 2 was substituted 5flourouracil with capecitabine, 2 taxane-platinum cycles (TP) and 5 cycles of chemotherapy line 2-line gemcitabine-carboplatin protocol) in combination With biological therapy with Cetuximab, the possibility of platinum re-challenge, the feasibility of the Capecitabine use of as a substituent of 5Fluorouracil, and the association of Cetuximab in the TPF protocol (so-called C-TPF protocol) with a favorable toxicity profile. A 24-month OS from the recurrence of the disease (local repalse or distant metastasis) using this aggressive regime is higher than the average OS at the recurrent or metastatic stage of head and neck squamous cell carcinoma (HNSCC)[4].

DISCUSSION

The TPE'x regimen includes Docetaxel (75 mg/m^2) and Cisplatin (75 mg/m^2) on day 1 and Cetuximab on days 1, 8 and 15. The initial dose of Cetuximab is 400 mg/m^2 on day 1 of cycle 1, followed by a 250 mg/m^2 weekly dose, over 4 cycles with granulocyte colony stimulating factor (G-CSF) as prophylaxis at each cycle being mandatory. If the disease is controlled after 4 cycles, cetuximab (500 mg / m^2) is given every 2 weeks until the disease progresses or has unacceptable toxicity. The EXTREME regimen includes 5-Flurouracil (4,000 mg/m^2) administered on days 1 to 4, Cisplatin (100 mg/m^2) on day 1. Cetuximab will be given as above every 21 days for six cycles (days 1, 8 and 15) and in case of a favorable response a 250 mg/m^2 dose cetuximab will be administered as maintenance treatment. It should be noted that the EXTREME regime does not include mandatory G-CSF[5-7].

The induction regimen based on the 3-cycle taxane-platinum-fluorouracil combination administered with 2-digit platinum-fluorouracil during radiotherapy showed good tolerance in a phase II study, but the substitution of Cisplatin with Carboplatin did not allow an evaluation of the benefit in term of survival and local control. IC in TPF protocol followed by CRT is considered a feasible and well tolerated treatment. The results of a study that included 48 patients with a chemotherapy completion rate of 85% highlights a rate of grade 3-4 toxicity (neutropenia) of 79% of which 15% febrile neutropenia. With a response rate of 79% IC followed by CRT it is considered a feasible and safe treatment option[8-9].

The randomized phase 3 PARADIGM trial led by Haddad and collaborators aims to demonstrate a possible OS benefit in adding 3 cycles of IC to standard chemo-radiotherapy treatment. Including 141 patients evaluated over a 49-month period, the study did not demonstrate a benefit of IC in term of OS. Grade 5 toxicity is considered comparable, but the rate of febrile neutropenia is much higher (16: 1) in the group that received IC versus the standard chemo-radiation. Although this trial is negative, Al Saraf et al. note the benefit obtained in the phase II trial with the triple combination of chemotherapy, a net benefit compared to the platinum-fluorouracil (PF) regimen supporting the re-evaluation of TPF regimen in a randomized phase III trial. The authors propose for evaluation an modified IC followed by the standard concurrent treatment. Is also mentioned the higher rate of toxicity (including mucositis, dehydration and nausea) as factors that advocate an attenuated regimen compared to the original TPF. The protocol named TCF in which Cisplatin is replaced with Carboplatin (AUC5) and 5-Fluorouracil in continuous infusion for 72 hours is replaced with 2,600 mg/m2 as 24 hour infusion on days 1, 8 and 15 is considered a feasible alternative to TPF IC followed by chemoradiation[10-11].

Substitution of Cipslatin with Carboplatin in HNSCC chemotherapy protocols is a controversial topic. Without being the subject of a randomized trials platinum doublet including Carboplatin, appears to be similar in efficacy, but with favorable toxicity profile compared with Cisplatin contain regimen. One of the first trial that evaluate Cisplatin replacement with Caboplatin was Volling's study showing a complete response rate of 33% in a group of 55 patients treated with IC combining Carboplatin and 5-Fluorouracil. Comparing the toxicity profiles, the authors note the lower rate of severe toxicity in Carboplatin doublet

arm comparing the results of the studies that combined Cisplatin and 5-Fluorouracil. A meta-analysis including 12 studies and 1165 patients comparatively evaluated the results of Cisplatin vs. Carboplatin in HNSCC. Favorable results in terms of OS and progression free survival (PFS) are obtained in groups of patients treated with Cisplatin, with no differences in the rate of recurrence, but subgroup analysis does not demonstrate the inferiority of Carboplatin in the case of NPC treatment. The toxicity profile differs, with Caboplatin being associated with a higher rate of hematological toxicity and a lower rate of nephrotoxicity and gastrointestinal toxicity compared to Cisplatin[12-13].

The substitution of 5-Fluorouracil with Capecitabine in the TPF induction protocol in HNSCC has been tested since 2013 in a phase I-II trial. At a dose of 500 mg/m^2 twice a day associated with 75 mg/m^2 Docetaxel and Cisplatin, the rate of grade 3 and 4 toxicity (neutropenia and diarrhea) was >50%, a dose of 750mg/m^2 daily being preferred for safety reasons. Cisplatin was also substituted with Cetuximab in combination with radiation therapy[14].

However, Iqbal and collaborators note that although there are phase I and phase II trials that demonstrate the feasibility and safety of substituting 5-Fluorouracil for Capecitabine, both in case of recurrence and as IC, with a special preference for fragile patients. The addition of a 400mg/m^2 dose of Cetuximab on the first day of the first TPF induction cycle followed by a weekly 250mg/m^2 dose was evaluated by Specenier and collaborators in a study that included stage III/IV un-resectable naso-pharyngal cancer patients. If there was no progression after induction regimen, patients were treated with bio- radiation therapy with Cetuximab, concurrent chemo-radiotherapy with weekly Cisplatin (40 mg/m2) or Carboplatin (AUC of 1.5 mg/ml/ min). Although antibiotic prophylaxis and G-GSF were administered, the high death rate from causes including septic shock and bowel perforation and severe toxicity led to the discontinuation of the study. Of the 46 patients, only 34 completed 4 cycles of TPF + Cetuximab and only 30 started bio-radiotherapy. The RTOG 0522 trial also provided disappointing results, confirming the concept that the addition of Cetuximab to chemo-radiotherapy with Cisplatin does not benefit OS and PFS, but increased the rate of toxicity[15-17].

In the case of breast cancer, the higher value of the nuclear antigen ki67 is already known to be a factor associated with lower OS and with an increased risk of loco-regional recurrence or distant metastasis. A cutoff value of 15% is considered predictive in discriminating the "high" versus "low" values of ki67. Zhao's study evaluated the response to radiation therapy for 108 patients with NPC depending of ki67 value. Radioresistance was associated with elevated ki67 values (80%). Only 47% of patients with an unfavorable response to irradiation had low ki67 values. The increased ki67 expression is considered by the authors to be associated with NPC radioresistance. Epidermal Grow Factor Receptor (EGFR) and p53 are also considered negative prognostic factors in NPC. A meta-analysis that included 20 literatures with 1545 patients confirms the association of EGFR expression in NPC with poorer OS and DFS, confirming the value of EGFR as a prognostic and predictive biomarker in nasopharyngeal carcinoma[18-22].

To compare the treatment results and late toxicities of Intensity Modulated Radiation Therapy (IMRT) with results obtained with conventional radiotherapy (2D-RT) or three-dimensional conformal radiotherapy (3D-CRT) in the case of definitive treatment with curative intent of NPC, a meta-analysis was performed including 3570 cases, with 1541 patients in the IMRT lot and 2029 in the patients' lot treated by 2D-RT or 3D-CRT techniques. The IMRT technique has been associated with superior OS and better local control at 5 years, but also with lower rates of late xerostomia, trismus and temporal lobe necrosis (TLN). A progression free rate by local recurrence of 90% has been reported since 2009 in a single institution phase II trial (Radiation Therapy Oncology Group Phase II Trial 0225), IMRT being considered superior to conventional radiotherapy both in combination with Cisplatin and as the only treatment method. The rate of toxicity including severe xerostomia associated with IMRT is also lower[23-24].

CSCO AND ASCO CURRENT RECOMMENDATIONS

A panel of experts from the Chinese Society of Clinical Oncology (CSCO) and the American Society of Medical Oncology (ASCO) proposed a series of recommendations for definitive chemo-radiotherapy of stage II-IVA nasopharyngeal carcinoma (NPC). Based on 108 studies considered relevant, the literature review was the support for the experts' opinion. Topics of interest were the sequence and type of chemothera-

py, IC options, adjuvant and concurrent chemotherapy and radiation therapy. The IMRT technique with daily imaging is unanimously the preferred option, and also there is the recommendation to transfer patients from department with 2D-RT and 3D-CRT techniques available to department that offer the IMRT irradiation method. The delivery of a total dose of 70Gy in 33-35 daily fractions of 2.12 respectively 2Gy by simultaneous integrated boost (SIB) or sequential boost technique is agreed, allowing a ballistic precision by using CT and MRI image guidance. Recommendations to consider as gross tumor volume (GTV) the volume delineated based on CT/MRI imaging before the administration of IC, image fusion between diagnostic imaging and simulation CT, omission of elective irradiation of lymph node level 1b if the tumor not involved the anterior half of the nasal cavity or there are no extranodal extension, no lymph nodes> 2 cm or no bilateral involvement in level II lymph nodes demonstrate the current refinement of image guided radiotherapy (IGRT) by using the IMRT technique in order to limit toxic effects. For patients with stage III-IVA except for T3N0, IC as an additional sequence for chemo-radiotherapy is recommended. If the induction sequence cannot be administered, chemotherapy after concurrent chemo-radiotherapy is recommended. A minimum two, recommended three cycles of Gemcitabine-platinum (GP) (Gemcitabine 1000 mg/m^2 day 1 day 8 and cisplatin 80mg/m^2 day 1) or TPF (Docetaxel 60-75mg/m^2 day 1 Cisplatin 60-75mg/m^2 day 1 and 5-Fluorouracil 600-750 mg / m^2 per day in continuous intravenous infusion from day 1 to day 5) are the recommended regimens, variants including taxanes-platinum (TP), platinum-Capecitabine (PX), platinum-fluorouracil (PF) are also options for IC. In adjuvant settings, the PF regimen administered at 4 weeks up to 3 cycles including Carboplatin (AUC 5) is considered an alternative in cases of contraindication for Cisplatin[28].

CONCLUSIONS

Induction and post-irradiation/radio-chemotherapy in TPF protocol, combination of TPF protocol with Cetximab, substitution of Cisplatin with Carboplatin and of 5Flurouracil with Capecitabine are options to be considered in selected cases. The unfavorable prognosis and the advanced stage of NPC are factors that justify an intensive treatment by poly-chemotherapy both in the first line or after disease recurrence. The higher toxicity rate of current treatment regimens explain the need of "modified" poli-chemotherapy protocols with or without biological therapy in order to keep the balance between therapeutic benefit and treatment toxicity. IMRT radiotherapy technique delivered by sequential boost or SIB in a total dose of 70Gy in 33-35 with daily imaging guidance should be offered as a standard to all patients with NPC treated with curative intent. Replacing 5-Floururacil with Capecitabine and of Cisplatin with Carboplatin may be an option to increase treatment tolerance and should be evaluated in randomized trials. The use of IC as a „new standard" before radio-chemotherapy for cases with unfavorable prognostic factors should also be the subject of future studies. Re-challenge with platiunum is also an option that needs to be re-evaluated.

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