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Commentary

Indirect comparison of TPF and GP induction chemotherapy regimens in nasopharyngeal carcinoma: a data-driven reassessment before the transition to induction chemoimmunotherapy

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Key words: nasopharyngeal carcinoma; induction chemotherapy; individual patient data; TPF; cisplatin gemcitabine.

Background

Nasopharyngeal carcinoma (NPC) is a rare cancer with a distinct geographic distribution, being endemic in Southern China, Southeast Asia (eg, Singapore, the Maldives, Indonesia, Malaysia, Vietnam), and Northern Africa.[1,2] Most NPC cases are associated with Epstein–Barr virus (EBV) infection.

High-level evidence has established concurrent chemoradiotherapy (CTRT) as the standard treatment for locoregionally advanced (LRA) NPC (a meta-analysis of chemotherapy on 26 trials and 7080 patients showed an absolute survival increase of 6.1% at 5 years, and 8.4% at 10 years, $P < .0001$), achieving a high local disease control rate (loco-regional failure dropped by 3.4% at 5 years, and by 3.7% at 10 years, $P = .0001$).[3] However, recurrence and distant metastases remain significant challenges. Given the chemosensitivity of this disease, induction chemotherapy (ICT) before CTRT has been explored as a strategy to enhance outcomes by reducing tumor burden and eradicating micrometastatic disease. An Individual Patient Data Network Meta-Analysis conducted on 20 clinical trials and 5144 NPC patients showed an absolute benefit of ICT over CTRT by 8.7% at 5 years.[4]

Several phase III trials have confirmed the superiority of ICT followed by CTRT over CTRT alone, demonstrating significant improvements in both progression-free (PFS) and overall survival (OS).[5,6]

ICT has also shown superior tolerability and compliance when added to CTRT compared to adjuvant chemotherapy, which is associated with higher risks of mucositis and hearing loss.[4]

Thus, international guidelines recommend induction for LRA NPC.[2,7,8]

However, only a few head-to-head studies have compared the 2 main ICT regimens, TPF (docetaxel, cisplatin, 5-fluorouracil) and platinum-gemcitabine (GP), especially in real-world settings,[9-13] and no large-scale prospective randomized controlled trials (RCTs) have been conducted to determine their differences in terms of outcomes. In everyday practice, clinicians must choose between TPF and GP based on their experience and the individual patient's condition, without strong high-level evidence to guide their decision. TPF has proven efficacy but is associated with significant toxicity (43% of grade 3-4 adverse events during the neoadjuvant phase, mostly leuco-neutropenia, and stomatitis; 73% in the overall treatment period including CTRT). In contrast, GP is a newer alternative, adapted from the metastatic setting, that offers comparable efficacy (hazard ratio for PFS 0.51 with GP, 0.68 with TPF; hazard ratio for OS 0.43 with GP, 0.59 with TPF) with the potential for reduced toxicity, especially in terms of leuco-netropenia and mucositis.

Furthermore, with the promising results of the Asian trials investigating chemoimmunotherapy as a neoadjuvant strategy, and its emergence as the new standard for LRA NPC,[14,15] there will be fewer opportunities to evaluate ICT regimens based solely on chemotherapy in the future. The occasion to reassess the existing evidence through a data-driven approach, leveraging existing phase III data, offers a unique chance to compare the efficacy and toxicity of available regimens before induction strategies evolve shortly.

Retrospective studies are prone to biases. Besides, reliable long-term data can also be sourced from previously published studies. In this context, extracting individual patient data (IPD) from published survival curves provides a practical approach to reconstructing survival trends. This method has the potential to generate sufficiently robust evidence to support indirect analyses, which may aid in clinical decision-making.

This article reports the analysis of pooled data extracted from the scientific papers of the 2 pivotal RCTs assessing the superiority of ICT followed by CTRT vs. CTRT alone in LRA NPC.

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Table 1. Summary of survival comparisons.

Arm	Measure	FFS	LRFS	DMFS	OS
Control (CTRT without induction CT)	*P* value (log-rank)	.414	.352	.861	.899
Experimental (ref TPF)	*P* value (log-rank)	.089	.813	.458	.41
	5-y-RMSTD (st.err)	2.763 (1.513)	0.128 (1.079)	1.15 (1.175)	1.857 (0.965)
	P value	*P* = .067	*P* = .905	*P* = .327	*P* = .054

Abbreviations: CT, chemotherapy; DMFS, distant metastasis-free survival; FFS, failure-free survival; LRFS, loco-regional recurrence-free survival; OS, overall survival; 5-y-RMST, restricted mean survival time difference at 5 years; st. err, standard error.

Methods

The clinical characteristics and the acute and late grade ≥ 3 adverse events of the comparator (ie, concomitant chemoradiation in the TPF and the GP trials) and experimental arms (ie, TPF vs. GP) of the 2 RCTs (TPF: Sun Y et al. Lancet Oncol 2016 and GP: Zhang Y et al. NEJM 2019) were compared through descriptive statistics, notably with Fisher's exact test using MedCalc Software. Although these comparisons should be regarded with criticism due to the innate bias of the AE reporting in different clinical trials, these comparisons were conducted to estimate a trend toward major differences in terms of safety between the 2 ICT regimens. Moreover, even if several other ICT regimens have been reported in the literature (eg, TP, TPC, etc.), the analyses concentrated on the 2 most broadly known in the literature and cited in clinical practice guidelines. IPD were reconstructed using the methodology outlined by Liu N et al.[16] Source data were extracted from the figures presented in the 2 RCTs. The failure/recurrence-free survival (FFS), loco-regional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were extracted from the first publications of the 2 clinical studies.[5,6] OS was reconstructed by digitalizing the curves published in the respective long-term follow-up final reports.[17,18] All the survival curves were digitized with the DigitizeIt software,[19] and the resulting CSV files containing the extracted x–y data points were subsequently uploaded to a Shiny application to obtain the inferred IPD.[16,20]

The following metrics were calculated to assess the accuracy of the reconstructed data: root mean square error, mean absolute error, maximum absolute error, and the *P*-value derived from the Kolmogorov–Smirnov test statistics. The finalized virtual database of IPD was analyzed using SAS® OnDemand for Academics. All survival curves were estimated via the Kaplan-Meier method and compared using the log-rank test. Comparisons were made between the comparator and experimental arms. The restricted mean survival time difference (RMSTD) at 5 years was estimated for each group.

Finally, a pooled analysis with the virtual dataset was conducted to characterize the benefit of the addition of induction chemotherapy in NPC across 2 large, randomized phase III trials.

Results

The clinical characteristics of patients randomized in the comparator arms did not differ significantly (Supplementary Table S1). At the same time (Supplementary Table S2), a statistically significant difference was observed in performance status (Karnofsky performance status 90%-100%: TPF 90% vs. GP 82%, *P* = .017) and primary tumor stage category (T1-T2: TPF 17% vs. GP 7%, *P* = .0009).

The frequency of grade ≥ 3 acute toxicities was similar between the 2 induction chemotherapy arms (Supplementary Table S3). Compared to subjects treated with TPF, those receiving GP had less frequent leukopenia (26% vs. 41%, *P* = .0009), neutropenia (28% vs. 42%, *P* = .001), and mucositis (29% vs. 41%, *P* = .005), but more anemia (10% vs. 2%, *P* = .0002) and thrombocytopenia (11% vs. 3%, *P* = .0002). No significant differences were observed in late toxicities (Supplementary Table S4).

Sixteen survival curves were reconstructed, 4s for each of the 4 groups of interest: FFS, LRFS, DMFS, and OS (Supplementary Figure S1) for the comparator and experimental arms of the TPF and the GP trials. The summary statistics of the digitalized curves are reported in Supplementary Tables S5 and S6. Survival analyses are summarized in Table 1.

The pooled analysis showed a statistically significant prolongation for induction chemotherapy over CTRT in terms of FFS, DMFS, and OS, and a trend towards significance for LRFS (Supplementary Figures S2–S5).

Discussion

IC plus CTRT has shown superiority to CTRT in the management of high-risk NPC in several RCTs; however, the optimal IC regimen has not been established at present. Furthermore, these studies showed that the tumor's response to IC could inform survival outcomes and might guide patients' personalized treatment.

Our indirect comparison suggests that GP may offer a slight survival advantage over TPF in OS, though statistical significance has not been reached. Patients included in the TPF trial had better performance status and lower disease stage than those enrolled in the GP RCT. These favorable characteristics could have turned into some prognostic advantage of TPF. Despite this positive bias, TPF did not perform better than GP in terms of patient outcomes. Indeed, the restricted mean survival time (RMST) analysis supports a trend toward a longer OS with GP.

Extracting data from the published papers made it impossible to infer IPD about plasma EBV DNA. The lack of comparison of this biomarker is one of the drawbacks of the current work. High levels of plasma EBV DNA are an adverse prognostic factor. Thus, this circulating biomarker is recommended as a practical selector and clinical stage to prescribe ICT.[2,8]

As far as treatment compliance and adverse events are concerned, GP was less toxic than TPF, particularly in terms of hematological toxicities. This better safety profile may

explain the observed trend toward better OS without relevant differences in FFS, LRFS, and DMFS. Indeed, the long-term survival detriment with TPF could be due to an increased non-cancer-related mortality, likely owed to the impact of treatment-related toxicities. Thus, balancing risks and benefits for IC in high-risk NPC is fundamental to avoid limitations on CTRT delivery, which remains the backbone of LRA NPC treatment.

Given similar efficacy but lower toxicity, GP might be the most favorable induction regimen in routine clinical practice. However, no direct comparison trial confirms this superiority, and clinical decision-making should be individualized, considering patients' characteristics (ie, performance status, comorbidities) and disease stage. Different international guidelines now recommend a GP regimen combined with immune checkpoint inhibitors as a first-line approach for recurrent/metastatic disease, and induction chemoimmunotherapy for non-metastatic LRA NPC has yet to become a new standard of care. Of note, a recent randomized trial conducted in the recurrent/metastatic setting has shown that a triplet regimen of nab-paclitaxel, cisplatin, and capecitabine outperformed gemcitabine plus cisplatin in terms of efficacy,[21] suggesting a potential role for taxane-based combinations that warrants further investigation in the induction setting.

The strengths of our data-driven reassessment include the comparison of phase III randomized data, which could minimize potential selection bias. Furthermore, the digitalization of Kaplan–Meier survival curves allows indirect reconstruction of IPD for advanced survival analyses.

Another opportunity was to characterize the benefit of adding induction chemotherapy to NPC across 2 significant randomized phase III trials. In this scenario, the pooled analysis with the obtained dataset confirmed the well-known survival improvement over CTRT alone.

However, a limitation of this method is the lack of direct access to IPD, which prevents adjustment for potential confounders. Additionally, the heterogeneity between the analyzed trials may introduce some variability despite similar eligibility criteria and treatment protocols. The lack of quality-of-life data and cost-effectiveness analyses limits the full assessment of the treatment burden.

A significant limitation that must be disclosed is that this work is a cross-trial comparison, including inherent bias, baseline differences, and selection bias. This aspect is particularly evident as far as safety is concerned. Indeed, AE capture is among the most poorly controlled elements in all clinical trials, even from 1 RCT to another.

Moreover, a disclaimer should be done citing the acronym "TPF." The actual regimen used in the RCT in NPC was substantially dose reduced relative to the TPF regimens developed in Europe and North America, and, currently, it is not so clear that this "TPF lite" is more toxic than GC. Adding up different AEs and grades and comparing them outside of a single RCT is likely to be skewed by so many factors as to be uninterpretable.

In conclusion, the role of induction therapy based only on chemotherapeutic agents will inevitably decrease because of the advent of a combination approach with immunotherapy. Our analysis represents one of the last opportunities to compare chemotherapy-based induction regimens before immunotherapy reshapes treatment algorithms and paradigms in LRA NPC.

Lastly, a relevant unanswered question is whether we can translate the results of clinical studies conducted in endemic areas to a non-endemic setting. All the knowledge of NPC's natural history is based on studies that have involved patients from Southern China and Southeast Asia, and the vast majority of clinical trials have been conducted in this setting. According to recent translational research based on transcriptomic analyses,[22] the similarities between the gene expression profiles of endemic and non-endemic NPC may also support the applicability of these results outside the endemic setting.

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The survival curves taken from the article Sun et al.[6] were reproduced with the permission of the publisher Elsevier (License Number 6054681106406). The survival curves taken from the article Li et al.[17] were reproduced with the permission of the publisher John Wiley & Sons (License Number 600215269). The survival curves taken from the article Zhang et al.[5] were reproduced with the permission of the publisher: given that the authors' intent was to prepare entirely new figures using data from the cited NEJM article, *The New England Journal of Medicine* is clearly acknowledged as a source, in compliance with the publisher's permission policies. The survival curves taken from the article Zhang et al.[18] are freely available as open access figures using the partial access granted by the *Journal of Clinical Oncology*.

Author contributions

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Conflicts of interest

Stefano Cavalieri discloses occasional fees for participation as a speaker at conferences/congresses from AccMed; support for attending meetings and/or travel from AccMed, MultiMed Engineers srl, Care Insight sas, unrelated to the content of this work. Lisa Licitra discloses the following conflicts of interest: research funds donated directly to the institute for clinical trials from AstraZeneca, BMS, Boehringer Ingelheim, Celgene International, Eisai, Exelixis, Debiopharm International SA, Hoffmann-La Roche Ltd, IRX Therapeutics, Medpace, Merck-Serono, MSD, Novartis, Pfizer, Roche, and Buran; occasional fees for participation as a speaker at conferences/congresses or as a scientific consultant for advisory boards from AstraZeneca, Bayer, MSD, Merck-Serono, AccMed, Neutron Therapeutics, Inc., and Alentis. Arianna Ottini and Benedetta Lombardi Stocchetti have no conflicts of interest to

disclose. All the Authors declare that the research reported in the current article was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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