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Original Article

Retrospective study on maintenance therapy with PD-1 inhibitor combined with S-1 or capecitabine after first-line treatment for recurrent or metastatic nasopharyngeal carcinoma

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Abstract: This study aimed to investigate the clinical efficacy and safety of programmed death-1 (PD-1) inhibitor combined with S-1 or capecitabine as maintenance therapy in patients with recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) following first-line systemic treatment. Clinical data of 95 patients diagnosed with R/M NPC were retrospectively analyzed. All patients were pathologically confirmed as having non-keratinizing undifferentiated NPC with metastatic lesions verified by imaging or pathological examination. After receiving at least 4 cycles of first-line treatment with PD-1 inhibitor combined with gemcitabine plus cisplatin chemotherapy regimen, patients entered the maintenance stage and were divided into two groups: the combination maintenance group (PD-1 inhibitor plus S-1 or capecitabine) and the PD-1 inhibitor monotherapy maintenance group. Baseline characteristics, objective response rate (ORR), disease control rate (DCR), changes of Epstein-Barr virus DNA (EBV-DNA) load, inflammatory indicators, nutritional status indicators, quality of life scores, adverse events, and survival outcomes were compared between the two groups. A logistic regression model was adopted to analyze the influencing factors of poor prognosis. After maintenance treatment, the secondary ORR and DCR were slightly higher in the combination maintenance group without statistical significance (both $P > 0.05$). The EBV-DNA negative conversion rate was significantly elevated in the combination group ($P < 0.05$). Inflammatory indicators of both groups were remarkably improved after treatment ($P < 0.05$). No significant inter-group differences were observed in nutritional status indicators, SF-36 quality of life scores, incidence and severity distribution of grade ≥ 3 adverse events, or immune-related adverse events (all $P > 0.05$). Progression-free survival (PFS) was significantly longer in the combination maintenance group ($P < 0.05$). Univariate logistic regression analysis showed that treatment regimen, EBV-DNA negative conversion rate and ECOG score were correlated with poor prognosis. Multivariate logistic regression analysis revealed that an ECOG score of 0-1 and EBV-DNA negative conversion rate were independent protective factors against poor prognosis. In conclusion, maintenance therapy with PD-1 inhibitor combined with S-1 or capecitabine after first-line treatment for R/M NPC yields definite therapeutic efficacy. The ORR and DCR showed an upward trend in the combination group, though the difference was not statistically significant. Meanwhile, this regimen can significantly elevate the EBV-DNA negative conversion rate, ameliorate systemic inflammatory responses and prolong PFS without increasing the risk of severe adverse reactions. Combined maintenance therapy did not trigger remarkable declines in most dimension scores of SF-36, and patients' overall quality of life remained relatively stable.

Keywords: Nasopharyngeal carcinoma, programmed death-1 inhibitor, S-1, capecitabine, maintenance therapy, Epstein-Barr virus DNA, inflammatory response, quality of life

Introduction

Nasopharyngeal carcinoma (NPC), a malignant tumor originating from the nasopharyngeal epithelium with obvious regional distribution, has a high incidence in southern China [1]. Although intensity-modulated radiotherapy has greatly improved the treatment outcomes of locally advanced NPC, some patients still develop local recurrence or distant metastasis after radical treatment, which remains a major clinical challenge [2]. Platinum-based dual-agent chemotherapy is currently the standard first-line regimen for recurrent or metastatic NPC

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(R/M NPC), yet its efficacy has reached a plateau with modest median progression-free survival (PFS). Cumulative chemotherapy-related toxicity also impairs patients' quality of life [3, 4]. With the development of immunotherapy, multiple studies have verified that gemcitabine plus cisplatin (GP) chemotherapy combined with PD-1 inhibitors can significantly prolong PFS and overall survival (OS), and elevate the objective response rate (ORR), which has become the new standard first-line treatment [5, 6]. Nevertheless, how to formulate subsequent maintenance therapy after 4 to 6 cycles of induction immunochemotherapy to maximize clinical benefits and delay disease progression has become a hot research topic.

PD-1 inhibitor monotherapy remains the predominant maintenance strategy at present, yet its efficacy varies widely, and early disease progression still occurs in a subset of patients [7]. Hence, exploring superior maintenance regimens to optimize patient prognosis is urgently needed. Both S-1 and capecitabine are oral fluoropyrimidine agents featuring convenient administration and favorable tolerability; they exert anti-tumor effects via inhibiting angiogenesis, activating anti-tumor immune responses and inducing direct tumor cell cytotoxicity [8]. Clinical reports on this combined regimen applied in the maintenance phase after first-line induction therapy for R/M NPC are limited. Given the synergistic mechanisms and respective clinical advantages of PD-1 inhibitors and oral fluoropyrimidines, this retrospective study analyzed the efficacy and safety of PD-1 inhibitors combined with S-1 or capecitabine in maintenance treatment, aiming to provide clinical evidence for therapeutic decision-making.

Materials and methods

Study design

This was a single-center, retrospective real-world study. Clinical data of patients diagnosed with R/M NPC admitted to the Eighth Affiliated Hospital of Guangxi Medical University between January 2020 and January 2024 were retrospectively analyzed. All data were extracted from hospital electronic medical records and follow-up files.

Study subjects and case selection

Inclusion criteria: (1) Pathologically confirmed non-keratinizing undifferentiated NPC by nasopharyngeal biopsy, with clinical stage IV disease; (2) Confirmed local recurrence or distant metastasis by imaging or pathological examination; (3) Received standard first-line induction therapy consisting of PD-1 inhibitor combined with gemcitabine plus cisplatin or nedaplatin for ≥ 4 cycles; (4) Achieved complete response (CR), partial response (PR), or stable disease (SD) after first-line induction therapy without radiological disease progression, and subsequently entered maintenance therapy; (5) Positive peripheral blood Epstein-Barr virus DNA (EBV-DNA) before maintenance therapy initiation, defined as an EBV-DNA load ≥ 50 copies/mL to ensure valid assessment of EBV-DNA negative conversion rate. (6) Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2, with adequate physical tolerance for subsequent maintenance therapy; (7) Maintenance therapy with either PD-1 inhibitor monotherapy or PD-1 inhibitor combined with oral S-1/capecitabine for at least one full cycle; (8) Complete clinical and follow-up data.

Exclusion criteria: (1) Concurrent primary malignant tumors of other organ origins; (2) Receipt of additional off-protocol antitumor therapies during maintenance treatment; (3) Failure to complete 4 cycles of first-line induction therapy or immediate switch to second-line therapy due to progressive disease during first-line treatment; (4) Prior treatment with any PD-1/PD-L1 inhibitors before study enrollment; (5) Severe hepatic or renal insufficiency, uncontrolled active autoimmune diseases or refractory active infections precluding tolerance to maintenance drugs; (6) Negative EBV-DNA status before maintenance therapy initiation; (7) Incomplete follow-up data or loss to follow-up.

Grouping method: Patients were divided into the PD-1 inhibitor monotherapy maintenance group (n=42) and the combination maintenance group (PD-1 inhibitor plus S-1 or capecitabine, n=53) according to assigned maintenance regimens. All patients received maintenance therapy immediately after first-line induction treatment, and none received second-line antitumor therapy during the maintenance period.

Sample size estimation: PFS was defined as the primary study endpoint. Referring to published clinical data of PD-1 inhibitor-based therapy for R/M NPC, the hazard ratio (HR) was assumed

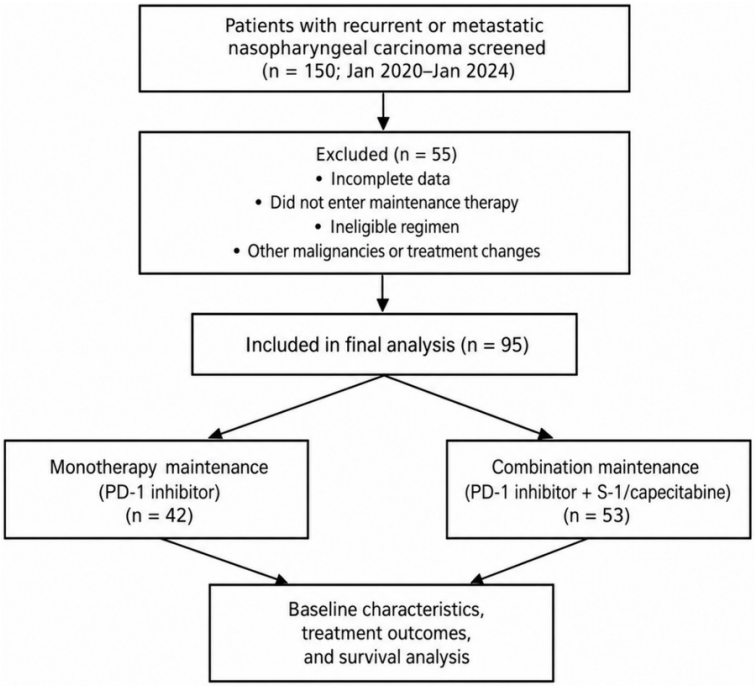

Figure 1. Flowchart of inclusion, exclusion and grouping of the research subjects.

to be 0.60, corresponding to a 40% reduction in the risk of disease progression [9]. Under a two-sided test with α=0.05 and statistical power of 80%, survival analysis indicated that approximately 88 PFS endpoint events were required. A total of 95 patients were finally enrolled, which met the statistical requirements for primary endpoint assessment.

This study was approved by the Ethics Committee of the Guigang City People's Hospital and complied with the principles of the Declaration of Helsinki. The ethics committee waived the requirement for written informed consent due to the retrospective study design and anonymization of all patient clinical data.

Treatment regimens and data collection

Maintenance regimens were comprehensively determined by attending physicians based on first-line treatment response, adverse reaction history, physical performance status, economic affordability and patient voluntary consent. All medication followed standard clinical practice guidelines. Clinical information including gender, age, ECOG performance status, metastatic sites, treatment protocols, EBV-DNA levels, radiological outcomes, adverse events and long-term follow-up data was retrospectively extracted from the hospital electronic medical system. The research flowchart is presented in **Figure 1**.

First-line treatment regimen: All patients received PD-1 inhibitor combined with GP chemotherapy. Gemcitabine (Sichuan Huiyu Pharmaceutical Co., Ltd., H20243258) was administered at 1000 mg/m^2 on days 1 and 8 of each cycle. Cisplatin (Qilu Pharmaceutical (Hainan) Co., Ltd., H20073652) 75 mg/m^2 or nedaplatin (Qilu Pharmaceutical Co., Ltd., H20050563) 80 mg/m^2 was administered on day 1. Camrelizumab (Suzhou Suncadia Co., Ltd, S20190027) was infused intravenously at 200 mg every 3 weeks. Each treatment cycle lasted 3 weeks, with a minimum of 4 cycles completed. Patients with confirmed CR, PR or SD entered the maintenance stage upon completion of first-line treatment.

Maintenance treatment regimen: The monotherapy group received camrelizumab at the identical dosage and administration frequency as first-line therapy. The combination group received camrelizumab plus oral S-1 (Qilu Pharmaceutical Co., Ltd., H20100150) or capecitabine (Jiangsu Hengrui Pharmaceuticals Co., Ltd., H20133365). S-1 was prescribed at 40-60 mg twice daily for 2 consecutive weeks followed by a 1-week rest period per 3-week cycle. Capecitabine was prescribed at 1000 mg/m^2 twice daily with the same 3-week cycle interval, for a total of 4 cycles. All dose adjustments, treatment delays, dose reductions and permanent drug withdrawals were documented, and causes of treatment interruption including disease progression, adverse events and other comorbidities were summarized.

Outcome measures

The primary endpoint was PFS, defined as the time from maintenance treatment initiation to disease progression or death. Secondary endpoints included OS, ORR, disease control rate

(DCR), EBV-DNA negative conversion rate, patient quality of life scores, and adverse events, particularly immune-related adverse events (irAEs).

Adverse events were graded per the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0) and categorized by affected organ systems including endocrine, cutaneous and gastrointestinal systems.

Clinical efficacy: Efficacy evaluation complied with Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) [10]. CR: disappearance of all target lesions, sustained for at least 4 weeks; PR: at least a 30% decrease in the sum of the longest diameters of target lesions relative to baseline; Progressive Disease (PD): at least a 20% increase in the sum of the longest diameters of target lesions relative to the lesion nadir, or the emergence of new metastatic lesions; SD: tumor status between PR and PD. The secondary ORR was defined as the proportion of patients achieving CR or PR, while DCR referred to the proportion of patients achieving CR, PR or SD. For secondary ORR and DCR assessments, lesion sizes measured immediately before maintenance therapy initiation were adopted as the new baseline, rather than the post-first-line treatment baseline. This adjustment objectively reflects tumor changes specific to the maintenance treatment phase. Similarly, a ≥ 50% reduction in tumor burden was defined as a ≥ 50% decrease in the sum of target lesion longest diameters relative to the pre-maintenance baseline.

Changes in EBV-DNA load: All enrolled patients had detectable EBV-DNA before maintenance therapy. Peripheral venous blood samples were collected at baseline and after 4 cycles of maintenance treatment. Real-time quantitative polymerase chain reaction (qPCR) was used to detect EBV-DNA loads via the Roche LightCycler® 480 II PCR instrument and supporting detection kits (Wenzhou Kemiao Biotechnology Co., Ltd). EBV-DNA negative conversion was defined as a viral load below 50 copies/mL, and negative conversion rates were compared between the two groups.

Inflammatory indicators: Blood specimens were collected at baseline and after 4 treatment cycles. Samples were centrifuged at 4500 r/min for 5 minutes with a centrifugal radius of 15 cm. C-reactive protein (CRP) was detected via immunoturbidimetry using the Roche Cobas c702 automatic biochemical analyzer. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated from routine blood test results measured by the Sysmex XN-9000 hematology analyzer.

Nutritional status indicators: Serum albumin (ALB) and prealbumin (PAB) levels were measured by the bromocresol green method and immunoturbidimetry respectively using the Roche Cobas c702 analyzer. Body weight changes before and after maintenance treatment were recorded synchronously.

Quality of life assessment: The 36-item Short Form Health Survey (SF-36), covering eight dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health), was used for assessment. Each dimension was scored from 0 to 100 points, with higher scores indicating better quality of life. Assessments were performed at baseline and after 4 maintenance cycles. A score change of 3-5 points was defined as the minimal clinically important difference for outcome interpretation. In this study, this range was adopted as an auxiliary threshold to determine whether changes in quality of life have potential clinical significance.

Adverse events: All adverse events occurring during the maintenance treatment window were documented, with focused monitoring of grade ≥ 3 severe toxicities including gastrointestinal and cutaneous reactions. IrAEs were graded from grade I to IV per CTCAE 5.0 criteria, and the incidence of organ-specific irAEs (endocrine, cutaneous, gastrointestinal, hepatic and respiratory) was statistically compared between groups.

Survival outcome: Radiological efficacy assessments were performed every 8-12 weeks during maintenance therapy; post-treatment survival follow-up was conducted once every 3 months. Follow-up methods included outpatient review and standardized telephone interviews. PFS and OS were compared between the two groups. All patients received a minimum of 18 months of follow-up, with the maximum follow-up duration exceeding 36 months. Patients lost to follow-up were censored at the date of their last valid follow-up.

Table 1. Comparison of baseline data between the two groups

Data	Monotherapy maintenance (n=42)	Combination maintenance (n=53)	$\chi^2/t/Z$	*P*
Gender (Male/Female)	30/12	39/14	0.055	0.815
Age (Years)	56.72±9.03	56.95±8.46	0.128	0.899
Disease Type (mmNPC/smNPC)	25/17	35/18	0.427	0.513
Body Mass Index (kg/m^2)	23.24±2.78	23.41±3.03	0.282	0.779
Metastatic Sites (Lung Metastasis/Liver Metastasis/Osteum Metastasis/Other)	12/14/12/3	15/19/15/4	0.169	0.866
ECOG Score (0-1 point/2 points)	35/7	40/13	0.871	0.351
Course of Disease (Years)	3.22±0.30	3.25±0.23	0.552	0.582

Note: mmNPC, metachronous metastatic nasopharyngeal carcinoma; smNPC, synchronous metastatic nasopharyngeal carcinoma; ECOG, Eastern Cooperative Oncology Group performance status.

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Group	CR	PR	SD	PD	ORR	DCR
Monotherapy maintenance (n=42)	2 (4.76)	26 (61.90)	8 (19.05)	6 (14.29)	28 (66.67)	36 (85.71)
Combination maintenance (n=53)	6 (11.32)	37 (69.81)	5 (9.43)	5 (9.43)	43 (81.13)	48 (90.57)
χ^2					2.597	0.539
P					0.107	0.463

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Statistical analysis

SPSS 25.0 software was used for all statistical analyses. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x}$±sd). Independent sample t-tests were used for inter-group comparisons, and paired t-tests for intra-group pre- and post-treatment comparisons; mean differences and corresponding paired t-values and *P*-values were reported for intra-group changes. Non-normally distributed continuous data were presented as median (interquartile range) with non-parametric tests for comparisons. Categorical data were expressed as case numbers and percentages [n (%)], and analyzed via the chi-square test or Fisher's exact test for small sample subsets. Kaplan-Meier curves were plotted for survival analysis, and the log-rank test was used for inter-group survival comparisons. Logistic regression was adopted to identify risk factors for poor prognosis. All statistical tests were two-tailed, and a *P*-value < 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

No significant inter-group differences were detected in all baseline variables (all P > 0.05). See **Table 1**.

Comparison of clinical efficacy

Secondary ORR and DCR showed no statistically significant inter-group differences (both P > 0.05). See **Table 2**.

Comparison of EBV-DNA load

Baseline EBV-DNA levels were balanced between the two groups (P=0.946). Post-treatment EBV-DNA loads also showed no inter-group difference (P=0.519). However, the combination group had a significantly higher EBV-DNA negative conversion rate (71.70% vs. 50.00%; χ^2=4.688, P=0.030). See **Table 3**.

Comparison of inflammatory response

CRP, NLR and PLR were comparable between groups at baseline (all P > 0.05). Intra-group paired t-tests confirmed significant reductions in all three inflammatory markers post-treatment in both groups. In the monotherapy group, the mean pre-post differences were -7.28±2.75 for CRP, -1.03±0.83 for NLR and -18.90±14.78 for PLR (paired t=-17.156, -8.042, -8.287; all P < 0.001). In the combination group, the mean differences were -7.48±2.90 for CRP, -1.09± 0.55 for NLR and -15.61±10.91 for PLR (paired t=-18.778, -14.428, -10.416; all P < 0.001). See **Table 4**.

Table 3. Comparison of EBV-DNA load changes between the two groups [M (P25, P75), copies/mL]

Indicators	Time	Monotherapy maintenance (n=42)	Combination maintenance (n=53)	z/χ^2	*P*
EBV-DNA load	Before treatment	1049.76 (938.55-1215.82)	1047.17 (962.74-1107.16)	-0.068	0.946
	After treatment	57.65 (37.77-77.49)	48.07 (41.35-73.73)	-0.644	0.519
EBV-DNA negative conversion rate		21 (50.00)	38 (71.70)	4.688	0.030

Note: EBV-DNA, Epstein-Barr virus DNA.

Table 4. Comparison of inflammatory responses between the two groups ($\bar{x}\pm s$)

Indicators	Group	Pre-treatment	Post-treatment	Difference (post-treatment minus baseline)	Paired t-test value	*P* value
CRP (mg/L)	Monotherapy maintenance (n=42)	11.52±2.63	4.40±1.35	-7.28±2.75	-17.156	< 0.001
	Combination maintenance (n=53)	11.81±2.40	4.32±1.21	-7.48±2.90	-18.778	< 0.001
NLR	Monotherapy maintenance (n=42)	2.58±0.65	1.53±0.51	-1.03±0.83	-8.042	< 0.001
	Combination maintenance (n=53)	2.60±0.53	1.50±0.46	-1.09±0.55	-14.428	< 0.001
PLR	Monotherapy maintenance (n=42)	146.72±21.55	127.83±17.55	-18.90±14.78	-8.287	< 0.001
	Combination maintenance (n=53)	144.62±19.64	128.92±15.08	-15.61±10.91	-10.416	< 0.001

Note: CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. Difference = post-treatment value - pre-treatment value; paired t-test was used for within-group comparisons pre- and post-treatment.

Table 5. Comparison of nutritional status between the two groups ($\bar{x}\pm s$)

Indicators	Group	Baseline	Post-treatment	Difference (post-treatment minus baseline)	Paired t-test value	*P* value
ALB (g/L)	Monotherapy maintenance (n=42)	38.64±4.50	38.12±3.97	-0.51±5.90	-0.560	0.578
	Combination maintenance (n=53)	39.11±3.77	38.55±3.20	-0.56±5.58	-0.731	0.468
PAB (g/L)	Monotherapy maintenance (n=42)	242.45±31.10	240.07±25.68	-2.39±43.44	-0.357	0.723
	Combination maintenance (n=53)	240.61±27.58	238.94±24.10	-1.68±39.76	-0.308	0.760
Weight (kg)	Monotherapy maintenance (n=42)	68.32±7.50	68.03±6.40	-0.29±8.61	-0.218	0.828
	Combination maintenance (n=53)	68.13±6.55	67.62±6.19	-0.51±9.19	-0.404	0.688

Note: ALB, albumin; PAB, prealbumin. Difference = post-treatment value - pre-treatment value; paired t-test was used for within-group comparisons pre- and post-treatment.

Comparison of nutritional status

Intra-group paired t-test revealed that there were no statistically significant changes in ALB, PAB and body weight after treatment compared with baseline in the monotherapy maintenance group, with mean differences of -0.51±5.90, -2.39±43.44 and -0.29±8.61, paired t-values of -0.560, -0.357 and -0.218, and *P*-values of 0.578, 0.723 and 0.828, respectively. Similarly, no statistically significant differences were observed in ALB, PAB and body weight before and after treatment in the combined maintenance group; the corresponding mean differences were -0.56±5.58, -1.68±39.76 and -0.51±9.19, paired t-values were -0.731, -0.308 and -0.404, and *P*-values were 0.468, 0.760 and 0.688. See **Table 5**.

Comparison of quality of life

Intra-group paired t-tests revealed that the social functioning score in the monotherapy group decreased after treatment compared with baseline ($P < 0.05$), while the changes in all other SF-36 dimension scores showed no statistical significance versus baseline (all $P > 0.05$). In the combination group, the general health score rose and the vitality score declined after treatment relative to baseline (both $P < 0.05$), and no statistically significant changes were observed in the remaining dimension scores compared with baseline (all $P > 0.05$). See **Table 6**.

Table 6. Comparison of quality of life between the two groups ($\bar{x}$±s, score)

Indicators	Group	Baseline	Post-treatment	Difference (post-treatment minus baseline)	Paired t-test value	*P* value
Physical Functioning	Monotherapy maintenance (n=42)	42.10±4.76	41.57±3.92	-0.53±4.40	-0.781	0.440
	Combination maintenance (n=53)	41.42±3.92	42.03±4.55	0.61±4.27	1.040	0.303
Role-Physical	Monotherapy maintenance (n=42)	43.46±4.33	42.52±3.77	-0.94±4.08	-1.494	0.143
	Combination maintenance (n=53)	42.76±4.65	42.33±4.20	-0.43±4.44	-0.705	0.484
Bodily Pain	Monotherapy maintenance (n=42)	40.47±4.33	40.99±3.42	0.52±3.95	0.852	0.399
	Combination maintenance (n=53)	41.05±3.77	41.44±4.40	0.39±4.12	0.689	0.494
General Health	Monotherapy maintenance (n=42)	38.32±4.12	39.11±3.44	0.79±3.83	1.338	0.188
	Combination maintenance (n=53)	39.03±3.55	40.12±4.20	1.09±3.92	2.027	0.048
Vitality	Monotherapy maintenance (n=42)	43.12±4.57	42.52±3.79	-0.60±4.23	-0.918	0.364
	Combination maintenance (n=53)	42.77±3.42	41.01±4.20	-1.76±3.87	-3.311	0.002
Social Functioning	Monotherapy maintenance (n=42)	44.79±4.12	43.20±5.16	-1.59±4.73	-2.180	0.035
	Combination maintenance (n=53)	43.92±3.44	43.57±4.30	-0.35±3.94	-0.647	0.521
Role-Emotional	Monotherapy maintenance (n=42)	43.04±4.33	42.52±3.55	-0.52±4.00	-0.843	0.404
	Combination maintenance (n=53)	43.42±3.78	42.83±4.20	-0.59±4.01	-1.072	0.289
Mental Health	Monotherapy maintenance (n=42)	44.55±4.16	43.52±3.45	-1.03±3.85	-1.732	0.091
	Combination maintenance (n=53)	43.89±3.40	44.11±4.55	0.22±4.10	0.391	0.698

Note: SF-36, 36-Item Short Form Health Survey; MCID, minimal clinically important difference. Difference = post-treatment value - pre-treatment value; paired t-test was used for within-group comparisons pre- and post-treatment.

Table 7. Comparison of adverse events between the two groups [n (%)]

Types of adverse events		Grading	Monotherapy maintenance (n=42)	Combination maintenance (n=53)	χ^2	*P*
Adverse events related to chemotherapy	Gastrointestinal toxicity	Grade III	1 (2.38)	2 (3.77)	0.042	0.837
	Skin and mucous membrane toxicity	Grade III	1 (2.38)	2 (3.77)	0.042	0.837
	Thrombocytopenia	Grade III	2 (4.76)	2 (3.77)	0.076	0.783
Immune-related adverse events	Endocrine system - Hypothyroidism	Grade I-II	6 (14.29)	9 (16.98)	0.128	0.721
	Hyperthyroidism	Grade I	2 (4.76)	2 (4.76)	0.076	0.783
	Skin system - Rash	Grade I-II	4 (9.52)	6 (11.32)	0.088	0.767
	Gastrointestinal system - Immune-related diarrhea	Grade I-II	1 (2.38)	2 (3.77)	0.042	0.837

Note: Grade I-II refer to mild to moderate adverse reactions, while Grade III and above are severe adverse reactions.

Comparison of adverse events

The incidence of grade ≥ 3 adverse events was similar between groups (P > 0.05). All recorded irAEs were grade I-II, with no grade IV irAEs reported. Organ-specific irAE incidence and severity distribution also showed no inter-group differences (all P > 0.05). See **Table 7**.

Comparison of survival outcomes

Kaplan-Meier survival analysis showed median PFS of 25.9 months (95% CI: 21.7 months-not reached) in the combination group and 16.8 months (95% CI: 13.8-22.3 months) in the monotherapy group. The 3-year OS rates were 79.2% (95% CI: 65.7%-87.9%) and 73.8% (95% CI: 57.7%-84.6%) respectively. The combination group achieved significantly prolonged PFS (P < 0.05). See **Figure 2**.

Comparison of clinical data among patients with different prognoses

Patients were stratified by the median OS of 39.6 months into the favorable prognosis group (≥ 39.6 months, n=57) and poor prognosis group (< 39.6 months, n=38), a standard stratification method in oncological prognostic research. Age, BMI, disease duration, sex, pathological subtype and metastatic site distribution were balanced between subgroups (all P > 0.05). Significant differences were found in maintenance regimen, ECOG score and EBV-

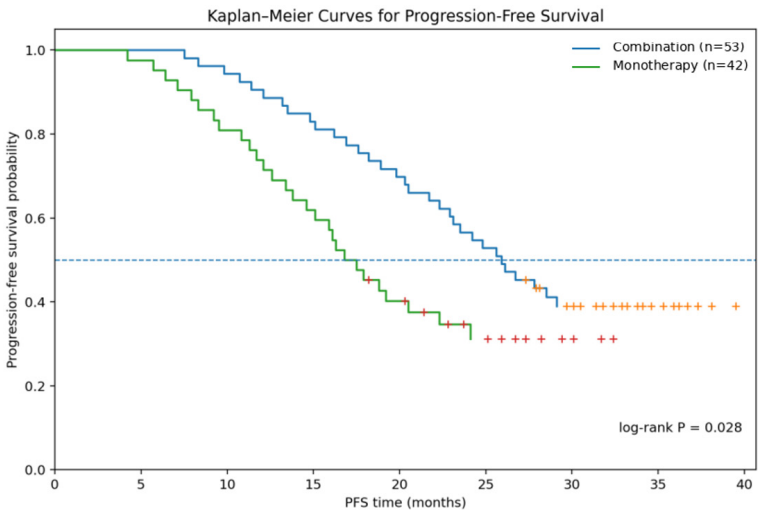

Figure 2. Kaplan-Meier survival curves of PFS for the two groups. The blue curve represents the combination maintenance group, and the green curve represents the monotherapy maintenance group. The "+" symbol indicates censored cases. Compared with the monotherapy maintenance group, the combination maintenance group shows a better survival trend in PFS. PFS, progression-free survival.

DNA negative conversion status (all P < 0.05). The poor prognosis group had higher rates of monotherapy use (60.5% vs. 33.3%), ECOG score of 2 (52.6% vs. 19.3%) and persistent EBV-DNA positivity (60.5% vs. 22.8%). See **Table 8**.

Univariate analysis of factors associated with poor prognosis

Univariate logistic regression identified three protective factors for reduced poor prognosis risk: combination maintenance therapy (OR= 0.326, 95% CI: 0.139-0.765, P=0.010), ECOG score 0-1 (OR=0.215, 95% CI: 0.086-0.538, P=0.001), and EBV-DNA negative conversion (OR=0.193, 95% CI: 0.079-0.473, P < 0.001). Age, BMI, disease duration, sex, pathological subtype and metastatic sites showed no prognostic correlation (all P > 0.05). See **Table 9**.

Multivariate analysis of factors associated with poor prognosis

Variables with P < 0.05 in univariate analysis were incorporated into the multivariate logistic regression model. ECOG score 0-1 (OR=0.133, 95% CI: 0.043-0.409, P < 0.001) and EBV-DNA negative conversion (OR=0.144, 95% CI: 0.049-0.427, P < 0.001) were confirmed as independent protective factors against poor prognosis. Maintenance regimen lost statistical significance after multivariate adjustment (P=0.066). See **Table 10**.

Construction of nomogram model for poor prognosis

A prognostic nomogram was established based on the two independent protective factors identified via multivariate logistic regression to quantify individual poor prognosis risk. Each variable was assigned a weighted score; total scores were summed to match corresponding poor prognosis probabilities on the risk axis. See **Figure 3**.

Model validation

The area under the receiver operating characteristic curve was 0.780 (95% CI: 0.690-0.871, **Figure 4A**), indicating good discriminatory power. Bootstrap internal validation with 1000 resamples yielded a C-index of 0.794 (95% CI: 0.715-0.876), confirming robust model stability. The calibration curve showed high consistency between predicted and actual prognosis outcomes, with a mean absolute error of only 0.031 (**Figure 4B**). Decision curve analysis (**Figure 4C**) demonstrated that the nomogram provided positive net clinical benefit when the threshold probability exceeded 20%, verifying its clinical applicability.

Discussion

Local recurrence and distant metastasis still occur in a subset of NPC patients after radical chemoradiotherapy, posing a critical clinical challenge [11]. The GP platinum-doublet regimen is globally recommended as first-line standard therapy, but it delivers limited median PFS and substantial acute toxicities [12, 13]. Recent prospective studies have confirmed that adding PD-1 inhibitors to GP regimens prolongs median PFS and improves ORR, making immunotherapy-based maintenance a mainstream post-induction strategy [14, 15]. However, PD-1 monotherapy maintenance often yields stagnant long-term efficacy [16]. An immunosup-

Table 8. Comparison of clinical data between the good and poor prognosis groups

Variable	Good prognosis group (n=57)	Poor prognosis group (n=38)	Statistical value	P
Age	56.75±8.00	56.97±9.69	-0.120	0.905
BMI	23.24±3.05	23.48±2.72	-0.385	0.701
Course of the disease	3.20 (3.10, 3.30)	3.30 (3.10, 3.40)	-0.767	0.438
Gender			0.432	0.511
Female	17 (29.8%)	9 (23.7%)		
Male	40 (70.2%)	29 (76.3%)		
Treatment plan			6.836	0.009
Monotherapy	19 (33.3%)	23 (60.5%)		
Combination	38 (66.7%)	15 (39.5%)		
Disease type			0.754	0.385
smNPC	23 (40.4%)	12 (31.6%)		
mmNPC	34 (59.6%)	26 (68.4%)		
Referred site			1.696	0.635
Lung metastasis	15 (26.3%)	12 (31.6%)		
Liver metastasis	19 (33.3%)	15 (39.5%)		
Bone metastasis	19 (33.3%)	8 (21.1%)		
Other	4 (7.0%)	3 (7.9%)		
ECOG score			11.524	0.001
2 points	11 (19.3%)	20 (52.6%)		
0-1 point	46 (80.7%)	18 (47.4%)		
EBV DNA negative conversion rate			13.783	0.000
No	13 (22.8%)	23 (60.5%)		
Yes	44 (77.2%)	15 (39.5%)		

Note: Prognostic grouping was stratified based on the median overall survival (OS) of 39.6 months in the entire cohort. Patients with OS ≥ 39.6 months were defined as the good prognosis group, and those with OS < 39.6 months were defined as the poor prognosis group. This grouping reflects actual survival outcomes and does not indicate that all patients in the good prognosis group have favorable baseline clinical characteristics. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; EBV-DNA, Epstein-Barr virus DNA.

pressed tumor microenvironment and persistent EBV-DNA positivity are two core barriers limiting survival benefits from single-agent immunotherapy.

This study found that the combination maintenance group achieved higher secondary ORR and EBV-DNA negative conversion rates than the monotherapy group. This suggests that PD-1 inhibitor combined with oral fluoropyrimidines enhances anti-tumor activity and accelerates EBV clearance in R/M NPC after first-line immunochemotherapy. The underlying mechanisms are multifactorial. Low-dose metronomic oral fluoropyrimidines inhibit thymidylate synthase to block tumor cell DNA replication, and deplete intracellular nucleotide pools required for EBV lytic replication, thereby suppressing viral shedding at the cellular level. Metronomic chemotherapy also normalizes disorganized tumor vasculature, relieves intratumoral hypoxia, and promotes cytotoxic T lymphocyte infiltration and activation, which synergizes with PD-1 immune checkpoint blockade [17].

Furthermore, fluoropyrimidines deplete immunosuppressive populations including regulatory T cells and myeloid-derived suppressor cells to reverse local immune tolerance. They also interrupt EBV nucleotide metabolism to inhibit viral reactivation and reduce peripheral EBV-DNA loads [18]. NPC tumor cells rely heavily on latent membrane protein 1 signaling; fluoropyrimidine-induced DNA damage upregulates tumor interferon signaling and MHC-I expression, alongside increased tumor PD-L1 expression, which further amplifies PD-1 inhibitor-mediated T-cell anti-tumor responses [19]. Steady oral drug concentrations sustain mild immune priming without causing effector T cell

Table 9. Univariate logistic analysis of factors affecting poor prognosis

Variable	*β*	*S.E*	*Z*	*P*	OR_95% CI
Age	0.003	0.024	0.122	0.903	1.003 (0.956-1.052)
BMI	0.028	0.072	0.389	0.697	1.029 (0.892-1.186)
Course of the disease	0.167	0.802	0.208	0.835	1.182 (0.245-5.694)
Gender					
Female					reference
Male	0.314	0.479	0.656	0.512	1.369 (0.536-3.502)
Treatment plan					
Monotherapy					reference
Combination	-1.121	0.435	-2.577	0.010	0.326 (0.139-0.765)
Disease type					
smNPC					reference
mmNPC	0.382	0.441	0.866	0.386	1.466 (0.617-3.480)
Referred site					
Lung metastasis					reference
Liver metastasis	-0.013	0.519	-0.026	0.980	0.987 (0.357-2.729)
Bone metastasis	-0.642	0.572	-1.121	0.262	0.526 (0.171-1.616)
Other	-0.065	0.856	-0.075	0.940	0.937 (0.175-5.022)
ECOG score					
2 points					reference
0-1 point	-1.536	0.467	-3.288	0.001	0.215 (0.086-0.538)
EBV DNA negative conversion rate					
No					reference
Yes	-1.647	0.458	-3.595	0	0.193 (0.079-0.473)

Note: BMI, body mass index; mmNPC, metachronous metastatic nasopharyngeal carcinoma; smNPC, synchronous metastatic nasopharyngeal carcinoma; ECOG, Eastern Cooperative Oncology Group performance status; EBV-DNA, Epstein-Barr virus DNA; PD-1, programmed death-1; S-1, tegafur, gimeracil and oteracil potassium.

Table 10. Multivariate logistic analysis of factors affecting poor prognosis

Variable	β	S.E	Z	*P*	*OR*_95% CI
Treatment plan					
Monotherapy					reference
Combination	-0.935	0.508	-1.839	0.066	0.393 (0.145-1.063)
ECOG score					
2 points					reference
0-1 point	-2.014	0.572	-3.522	< 0.001	0.133 (0.043-0.409)
EBV DNA negative conversion rate					
No					reference
Yes	-1.936	0.553	-3.499	< 0.001	0.144 (0.049-0.427)

Note: ECOG, Eastern Cooperative Oncology Group performance status; EBV-DNA, Epstein-Barr virus DNA; OR, odds ratio; 95% CI, 95% confidence interval; S.E, standard error, Z, Z statistic; reference, reference group.

depletion associated with high-dose intermittent chemotherapy, achieving low-toxicity synergistic treatment.

In this study, maintenance regimen, EBV-DNA negative conversion and ECOG score as OS-related factors. Logistic regression verified combination maintenance therapy and EBV-DNA clearance as independent OS protective factors, while ECOG score of 2 was an independent poor prognostic factor. The survival benefit of combined maintenance therapy is largely

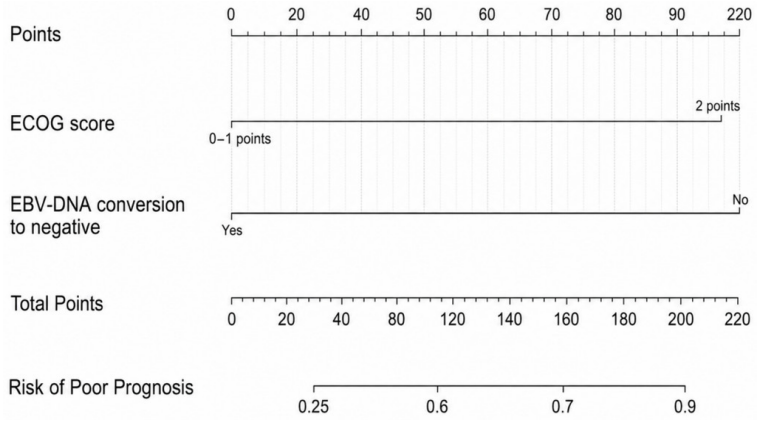

Figure 3. Risk nomogram for poor prognosis of nasopharyngeal carcinoma. ECOG, Eastern Cooperative Oncology Group performance status; EBV-DNA, Epstein-Barr virus DNA; OR, odds ratio; CI, confidence interval.

attributed to residual microscopic tumor clearance and sustained EBV suppression, a key oncogenic driver of NPC progression. As an objective indicator of patients' general physical status, a higher ECOG score usually indicates poorer treatment tolerance and diminished therapeutic response potential, which explains its identity as an independent adverse prognostic factor.

Systemic inflammatory markers improved significantly in both groups post-treatment. Unlike high-dose conventional chemotherapy, metronomic low-dose fluoropyrimidines do not trigger systemic inflammatory cytokine storms. Tumor burden reduction and EBV antigen clearance jointly alleviate chronic tumor-associated systemic inflammation in both treatment cohorts [19].

Nutritional indicators, SF-36 quality of life scores, grade ≥ 3 adverse event rates and irAE profiles showed no inter-group differences. Patients tolerated combined maintenance well after intensive first-line therapy, as metronomic dosing avoids the fluctuating systemic toxicity of conventional cytotoxic chemotherapy and preserves physical function and quality of life [20]. The superior PFS in the combination group confirms its clinical prognostic advantage.

This study has inherent limitations of retrospective single-center design, including potential selection bias. Although sample size was calculated based on expected PFS events, actual observed endpoint events were fewer than projected, which may reduce statistical power for negative secondary endpoint findings such as DCR and quality of life. The optimal dosage and treatment duration of S-1 and capecitabine in NPC maintenance regimens remain undefined, requiring large-scale prospective multicenter validation. Additionally, only patients with pre-maintenance EBV-DNA positivity were enrolled to standardize negative conversion endpoint assessment. Therefore, study conclusions are only generalizable to EBV-DNA-positive R/M NPC patients initiating maintenance therapy. Extrapolation to patients with baseline EBV-DNA negativity requires further dedicated validation. Notably, several patients in the favorable prognosis subgroup had baseline ECOG 2 scores, which is not contradictory. Post-hoc OS-based prognostic stratification incorporates dynamic on-treatment factors rather than only baseline physical status; patients with poor baseline performance may achieve prolonged survival via effective maintenance therapy and EBV clearance. This confirms that R/M NPC prognosis is determined by multiple interacting clinical factors rather than ECOG score alone.

In conclusion, PD-1 inhibitor combined with S-1 or capecitabine is an effective and safe maintenance regimen for R/M NPC after first-line immunochemotherapy. It improves EBV-DNA negative conversion rate, alleviates systemic inflammation and prolongs PFS and OS without increasing severe toxicity risks. Combined maintenance therapy and EBV-DNA clearance are independent protective factors for long-term survival, with no detrimental impacts on patient nutrition or quality of life.

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Disclosure of conflict of interest

None.

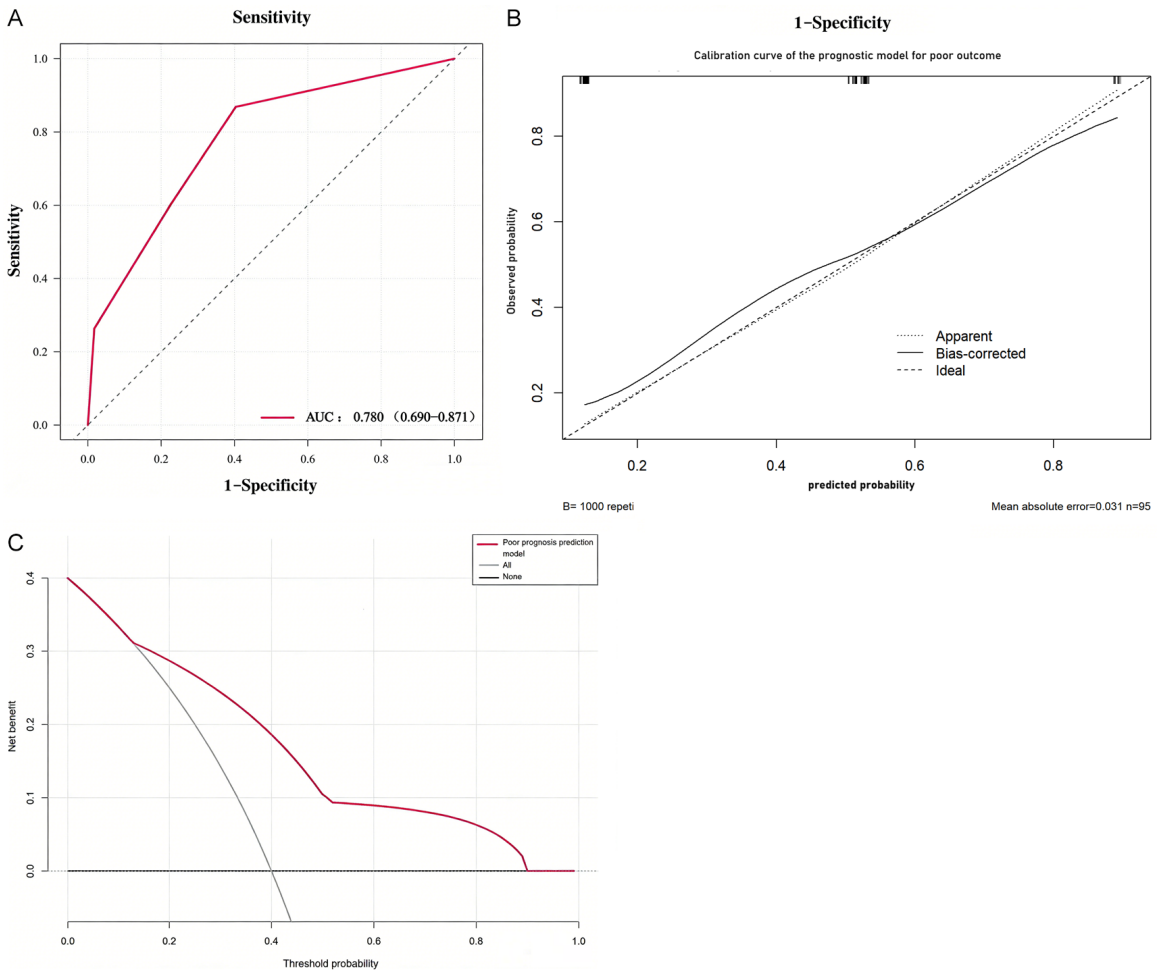

Figure 4. ROC, calibration and clinical decision curves of the risk prediction model for poor prognosis of nasopharyngeal carcinoma. Note: (A) ROC curve of the nomogram model for predicting poor prognosis of nasopharyngeal carcinoma; (B) Calibration curve of the nomogram model for predicting poor prognosis of nasopharyngeal carcinoma; (C) Clinical decision curve of the nomogram model for predicting poor prognosis of nasopharyngeal carcinoma. The decision curve shows the clinical net benefit of applying this prediction model at different threshold probabilities. All: intervention for all patients; None: no intervention for any patient; Model: this nomogram model guides the decision. ROC, receiver operating characteristic curve; AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group performance status; EBV-DNA, Epstein-Barr virus DNA; CI, confidence interval.

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