ASCO 2021 highlights head and neck cancer: nasopharyngeal carcinoma

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Summary During the ASCO 2021 virtual meeting, multiple clinically relevant studies were presented addressing open questions regarding the therapy of nasopharyngeal carcinomas (NPC): Is immunotherapy plus chemotherapy the new first line standard of care for patients in the recurrent/metastatic setting? Is adjuvant therapy with capecitabine in high risk NPC patients post chemoradiation (CRT) beneficial? Is there a role for treatment intensification by adjuvant metronomic capecitabine in NPC patients post induction chemotherapy and CRT? This article summarizes the most significant NPC studies presented at the ASCO 2021 virtual meeting and discusses the data in the context of the current literature.

Keywords Nasopharyngeal carcinoma · Immunotherapy · Adjuvant therapy · Toripalimab · Camrelizumab · Capecitabine

Introduction

During the virtual American Society of Clinical Oncology (ASCO) 2021, scientific meeting several interesting studies in the field of head and neck cancer were reported. In particular clinical trials conducted in locally advanced and metastatic nasopharyngeal carcinoma (NPC) investigating either novel strategies in the adjuvant setting or novel compounds in stage I/II disease might be potentially practice changing in the future and are reviewed in this manuscript.

Metastatic NPC

JUPITER-02 trial: immunotherapy with toripalimab plus chemotherapy vs. chemotherapy alone [1]

This multicenter randomized double-blind placebo controlled phase III study presented at the plenary session included 289 patients suffering from treatment naïve recurrent/metastatic (R/M) NPC. Patients were randomized to a standard of care (SoC) arm (143 patients) receiving chemotherapy with cisplatin/gemcitabine (GP) plus placebo and to an experimental group (146 patients) receiving GP plus toripalimab, a humanized programmed death receptor-1 (PD-1) monoclonal antibody. Chemotherapy was given for up to six cycles followed by placebo or toripalimab maintenance. Baseline characteristics were well balanced between the arms. Of note, the majority of patients (99%) suffered from World Health Organization (WHO) type II/III NPC and were PD-L1 positive (75%). The primary endpoint was progression-free survival (PFS) and was met. The PFS in the GP+ toripalimab arm was 11.7 months vs. 8.0 months in the SoC group (HR: 0.52; 95% CI: 0.36–0.74; $p=0.0003$). The benefit was seen across all subgroups including PD-L1-negative patients (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.15–0.81) or patients with an Epstein–Barr virus (EBV) copy number above 2000 (HR 0.46; 95% CI 0.3–0.72). Overall survival (OS) data are not mature yet and no statistically significant difference between the treatment arms was observed (HR 0.603; 95% CI 0.364–0.997; $p=0.0462$). Apart from that, both duration of response (DoR) and overall response rate (ORR) was longer/higher in the experimental arm (DoR: 10.0 vs. 5.7 months; ORR 77.4% vs. 66.4%). The side effect profile was well manageable and no new safety issues were reported.

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CAPTAIN-1st trial: immunotherapy with camrelizumab plus chemotherapy vs. chemotherapy alone [2]

The multicenter randomized double-blind placebo-controlled Chinese CAPTAIN-1st III study aimed at demonstrating the superiority of GP plus the PD-1 inhibitor camrelizumab over GP plus placebo in untreated R/M NPC. The study design, maintenance therapy and endpoints were similar to the aforementioned JUPITER-02 study. In total, 263 patients (SoC: 129 patients; camrelizumab/GP: 134 patients) were randomized. The median PFS in the camrelizumab plus GP group was 10.8 months and superior to the PFS in the GP arm (6.9 months; HR 0.51; 95% CI 0.37–0.69; $p < 0.0001$). Likewise, the PFS benefit was observed across all subgroups. In contrast to the JUPITER-02 study, the PD-L1 status of the study population was not reported. Addition of camrelizumab to SoC did not result in a statistically significant OS benefit yet and a longer follow-up time is needed to draw a final conclusion (OS not reached vs. 22.6 months for the SoC group; HR 0.67; 95% CI 0.41–1.11). GP plus camrelizumab resulted in a higher ORR (88.1%) compared to GP (80.6%). DoR was longer in the experimental arm than in the SoC arm (9.9 months vs. 5.7 months; HR 0.48; 95% CI 0.34–0.68; $p < 0.0001$). Toxicity was similar to what was reported in previous camrelizumab plus chemotherapy studies. The high rate (up to 60%) of grade I/II reactive capillary hemangiomas (RCEPs), which is well described for camrelizumab therapy, is worth mentioning despite being well manageable.

Maintenance capecitabine plus best supportive care versus best supportive care [3]

A single center open label randomized phase III study evaluated the role of capecitabine (1250 mg/m² bid) maintenance therapy administered after 4–6 cycles induction chemotherapy (cisplatin/paclitaxel) vs. best supportive care in newly diagnosed R/M NPC patients. A total of 140 patients were randomized. The primary endpoint was PFS and was met. The PFS in the capecitabine arm was superior to the SoC group (35.2 months vs. 9.1 months; HR 0.426; 95% CI 0.248–0.731; $p = 0.0001$). Toxicity was well manageable in the capecitabine group.

Locally advanced NPC

Metronomic capecitabine as adjuvant therapy [4]

The efficacy and safety of metronomic capecitabine 650 mg/m² bid given for up to 1 year vs. observation in patients with locally advanced high-risk NPC treated with curative chemoradiation was investigated in a randomized controlled phase III trial presented during the oral abstract session. Stage III-

IVA NPC patients (excluding T3-4 N0 and T3N1) were eligible to receive metronomic capecitabine vs. observation. Primary endpoint was failure-free survival (FFS) at 3 years. Secondary endpoints included OS, distant FFS and locoregional FFS. Prior induction chemotherapy (IC) was allowed. In total 406 patients were randomized (204 and 202 per arm) and the majority was exposed to IC (77%). The study was positive and reached all endpoints, since metronomic capecitabine improved FFS (85.3% vs. 75.7%; HR 0.5; 95% CI 0.32–0.79; $p = 0.002$), OS (93.3% vs. 88.6%; HR 0.44; 95% CI 0.22–0.88; $p = 0.018$), distant FFS (89.4% vs. 82.1%) and locoregional FFS (92.6% vs. 87.8%) compared to observation. A benefit across all subgroups was observed. The toxicity profile was beneficial and hand-foot syndrome the most common adverse event (58%).

Standard dose capecitabine as adjuvant therapy [5]

In contrast to the study outlined above, eight cycles of standard dose (1000 mg/m² bid) capecitabine were administered in the experimental arm of a similar randomized controlled phase III in high-risk locally advanced NPC patients treated with curative intent. Besides tumor stage, additional risk factors such as EBV DNA > 20,000 copies/ml, high tumor volume, multiple neck node metastases or a maximum standard uptake value > 10 as measured by PET-CT was required for eligibility. Patients exposed to prior IC were excluded. FFS at 3 years was the primary endpoint. In all, 180 patients (90 per arm) were randomized. FFS was superior in the capecitabine arm compared to the observation group (87.7% vs. 73.3%; HR 0.52; 95% CI 0.29–0.97; $p = 0.037$). However, secondary endpoints such as OS, locoregional recurrence-free survival or distant-metastasis-free survival were not met or are immature.

Discussion

NPC is endemic in southern China and Hong Kong with an incidence of approximately 25 cases per 100,000, while it is regarded as an orphan disease in the western world [6–8]. In the endemic regions NPC is mainly associated with EBV infection, whereas in the USA and Europe alcohol and tobacco use comprise the major risk factors for NPC development [9, 10]. From this background, it seems obvious why no large randomized phase III studies have been performed outside endemic areas. The current NPC treatment guidelines are mainly based on the evidence generated by clinical trials conducted in Asia resulting in underrepresentation of WHO type I NPC patients.

In the R/M setting GP is the SoC first-line approach irrespective of the subtype resulting in a median PFS and OS of 7 and 29 months, respectively [11]. Since NPC is regarded as an immunogenic malignancy char-

acterized by high rates of tumor-infiltrating lymphocytes, multiple single arm phase II studies evaluated the efficacy of immune checkpoint inhibitors such as pembrolizumab, nivolumab or toripalimab in the second-line R/M setting [12–16]. Based on the promising outcomes of these studies it is not surprising that attempts have been made to transfer immunotherapy to earlier lines and combine it with chemotherapy. Although Jupiter-02 and Captain-1st clearly support this approach, a couple of open questions and limitations remain: (1) The PFS curves overlap during concurrent immunotherapy plus chemotherapy phase and separate during maintenance therapy. This finding suggests that an active comparator such as gemcitabine would have been important in the control group. (2) OS data are immature and it is unclear whether immunotherapy plus chemotherapy resulted in an OS benefit in R/M NPC patients compared to SoC. (3) Neither toripalimab nor camrelizumab are approved outside of Asia and substitution of those agents by any available checkpoint inhibitor does not seem to be justified.

Therefore, the combination of immunotherapy with chemotherapy in untreated R/M NPC remains investigational until a more widespread regulatory approval and additional follow-up is available.

As for high-risk locally advanced NPC, the SoC approach (IC followed by chemoradiation [CRT] or CRT followed by adjuvant chemotherapy) results in a 3-year FFS of approximately 80% [17–19]. Especially the role of adjuvant chemotherapy in patients who did not undergo IC is still a matter of debate and associated with considerable toxicity.

Both capecitabine trials presented promising data. However, it is surprising that the FFS in the metronomic and standard dose capecitabine studies outlined above are comparable despite more intensive treatment with IC in the metronomic capecitabine study. To identify patients who derive a benefit from adjuvant capecitabine, use of a predictive biomarker is highly desirable. Since a recent study investigating the role of postradiation EBV DNA as a biomarker for adjuvant chemotherapy did not show a difference with respect to relapse-free survival, further research is needed and the use of EBV DNA to select patients for adjuvant therapy is not recommended outside clinical trials [20].

Conclusion

Despite its chemo- and radiotherapy-sensitive tumor biology, the treatment of NPC remains a clinical challenge. The outcomes in the R/M setting are poor and adjuvant therapy after CRT is not tolerated by the majority of the patients. Therefore, the immunotherapy and adjuvant capecitabine phase III NPC studies presented during the virtual ASCO 2021 conference will potentially change clinical practice depending on the outcomes of longer follow-up.

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