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The Management of Advanced Anal Squamous Cell Carcinoma

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Introduction

Cancers of the anal canal are rare malignancies defined anatomically from the anorectal junction to the perianal region.[1,2] The most common histotype is anal squamous cell carcinoma (ASCC), which represents 1%–2% of all gastrointestinal cancers.[1] Despite recent advances in the treatment of modifiable risk factors, the incidence of ASCC continues on a slow but unabated upward trajectory driven by predisposing factors including smoking, human papillomavirus (HPV) and human immunodeficiency virus (HIV) infections, and immunosuppression, amongst others.[1,2] Metastatic ASCC (mASCC), either *de novo* stage IV disease or distant recurrence following definitive concurrent chemoradiation, is also increasing in frequency, representing 10%-30% of all diagnoses.[1,2] While localized disease is curable with chemoradiation, using mitomycin-c and fluoropyrimidine-based sensitizing chemotherapy, advanced or metastatic disease is associated with significantly worse outcomes and a historical median overall survival (OS) below 20 months and 5-year OS between 19%–30%.[3,4] The management of advanced or metastatic ASCC has undergone significant changes in the past decade, and herein we will highlight the current treatment paradigm and future directions in this field.

Overview of Advanced ASCC Treatment in the First-line Setting

Owing to the relative rarity of advanced ASCC and the consequent difficulty enrolling patients into randomized trials, there have historically been few treatment options with robust prospective data in this setting. Available options were extrapolated from other squamous cell carcinomas (SCCs), retrospective case series, and small single-arm phase II trials.[5-11] Platinum-based combinations, typically cisplatin with 5-fluorouracil (5-FU), were commonly used, albeit with moderate objective response rates (ORR) ranging from 30%-60%, limited duration of response (DOR), and often significant toxicities including neuropathy, myelosuppression, febrile neutropenia, and mucositis, requiring frequent dose-modifications or treatment interruptions.[5-11] Overall, the combination of poor patient tolerance, limited OS, and scarce prospectively validated regimens led to international collaborations for the development of subsequent clinical trials.

In 2020, the International Rare Cancers Initiative Anal Cancer Working Group conducted the landmark InterAAct trial. This was an international, prospective, randomized, phase II study of 91 previously untreated patients with advanced or mASCC, comparing 5-FU and cisplatin versus carboplatin and paclitaxel in a pick-the-winner design with ORR as the primary endpoint.[12] While no difference in ORR was detected, as it was 57% (95% confidence interval [CI], 39.4%-73.7%) for cisplatin and 5-FU versus 59% (95% CI, 42.1%-74.4%) for carboplatin and paclitaxel, the carboplatin arm exhibited fewer grade ≥3 adverse events (36% versus 62%; p=0.016), resulted in a numerically superior progression-free survival (PFS) of 8.1 months (95% CI, 6.6-8.6) versus 5.7 months (95% CI, 3.3-9.0) and an OS of 20 months (95% CI, 12.7-not reached) versus 12.3 months (95% CI, 9.2-17.7), with a hazard ratio (HR) of 2.00 (95% CI, 1.15-3.48; p=0.014). Therefore, this trial established carboplatin and paclitaxel as the preferred first-line chemotherapy regimen in this setting.[12]

Building on this, recent efforts have focused on a pathogenesis-informed, biomarker-driven approach to clinical trial development underpinned by improved understanding of ASCC biology.[6] HPV infection is present in >90% of ASCC cases, and carcinogenesis is driven by HPV-16 and HPV-18, which produce viral oncoproteins E6 and

E7 that disrupt p53 and retinoblastoma tumour suppressor functions and promote resultant cell proliferation and genomic instability.[13,14] Despite a relatively low tumour mutational burden, HPV-associated cancers are immunologically "hot", exhibiting dense infiltration of cytotoxic T cells and tumour-infiltrating lymphocytes, transforming growth factor (TGF)-β and interferon (IFN)-ɣ upregulation, increased antigenicity, and higher programmed death ligand 1 (PD-L1) expression.[13,14] Patients living concurrently with HIV and mASCC likewise exhibit an immunophenotype potentially amenable to immunotherapy (IO) treatment, with an increased density of $CD8^+$ T cells in the tumour microenvironment (TME) even when viral replication is suppressed.[13,14] Together, these observations provided the rationale for the use of IO in recent practice-changing clinical trials.

The POD1UM-303/InterAAct-2 trial was a landmark global randomized, controlled, double-blind phase III clinical trial including 308 previously untreated patients with inoperable locally advanced ASCC or mASCC that evaluated the immune checkpoint inhibitor (ICI) retifanlimab (an anti-programmed cell death protein 1 [PD-1] antibody) in addition to carboplatin and paclitaxel versus carboplatin and paclitaxel monotherapy in the first-line setting.[15] Previous chemotherapy concurrent with radiotherapy was permitted in the neoadjuvant/adjuvant setting if completed 6 months or more prior to entry of the study. Notably, in the initial phase II InterAAct trial cohort, of the 45 patients randomized to carboplatin and paclitaxel, 70% were female with median age of 61, and 89% of patients had metastatic rather than locally advanced disease, an Eastern Cooperative

Trial	Patient population	Treatment line	Sample size (N)	Regimen and Comparator	ORR % (95% CI)	Median PFS (months)	Median OS (months)
InterAAct[12]	Metastatic or recurrent ASCC	1L	91	Carboplatin + paclitaxel	59% (42.1-74.4)	8.1	20.0
				Cisplatin + 5-FU	57% (39.4-73.7)	5.7	12.3
POD1UM-303/ InterAAct-2[15]	Metastatic or recurrent ASCC	1L	308	Retifanlimab + carboplatin + paclitaxel	56% (47.6-63.8)	8.3	29.2 (initial publication)
				Carboplatin + paclitaxel	44% (36.2-52.4)	6.2	23.0 (initial publication)
POD1UM-202[21]	Previously treated ASCC	≥2L	94	Retifanlimab (single-arm trial)	13.8% (7.6-22.5)	2.3	10.1
KEYNOTE-158 (ASCC)[22]	Advanced ASCC, PD-L1 not selected	≥2L	112	Pembrolizumab (single-arm trial)	11% (6-18)	2.0	12.0
NCI9673 – Part B[23]	Refractory metastatic ASCC	≥2L	37	Nivolumab ± ipilimumab	24% (15-33)	4.1	11.5

Table 1. Selected Trials on the Management of Advanced ASCC; *courtesy of Vladimir Djedovic, MD, MSc, FRCPC, Donald Bastin, MD, MSc, and Michael Vickers, MD, MPH, FRCPC.*

Abbreviations: 1L: first-line; **2L:** second-line; **ASCC:** anal squamous cell carcinoma; **CI:** confidence interval; **ORR:** objective response rate; **OS:** overall survival; **PD-L1:** programmed death ligand 1; **PFS:** progression-free survival.

Oncology Group performance status (ECOG PS) of 1, and 4% were HIV-positive, with 26 of 45 patients having received induction chemoradiation therapy previously. In the InterAAct-2 study, the cohort was quite similar, with >70% females, a median age of 61, predominantly white Europeans (>90% of the cohort), 82% had metastatic rather than locally recurrent disease, the majority of patients had ECOG PS of 0-1, and 3% were HIV-positive. A notable difference between the trials is that PD-L1 expression testing was performed only in the InterAAct-2 trial and revealed that 91% of patients had PD-L1 expression ≥1, as determined by the SP263 PD-L1 immunohistochemistry assay.

In the InterAAct-2 trial, the primary endpoint was PFS, with OS and safety as key secondary endpoints.[15] The retifanlimab arm had improved PFS, with a median PFS of 9.3 months (95% CI, 7.5-11.3) versus 7.4 months (95% CI, 7.1-7.7), resulting in a HR of 0.63 (95% CI, 0.47-0.84; one-sided p=0.0006). Likewise, the ORR was 55.8% (95% CI, 47.6%-63.8%) versus 44.2% (95% CI, 36.2%-52.4%; p=0.013), and median DOR of 14 months (95% CI, 8.6-22.2) versus 7.2 months (95% CI, 5.6-9.3), all favouring the retifanlimab combination arm.[15] At the time of this publication, the median OS of this study was 32.8 months (95% CI, 24.2-not estimable) versus 22.2 months (95% CI, 15.1-27.9) in the chemotherapy-alone arm, with a HR of 0.70, but these data remain immature.[15] The observed benefits of the combination treatment were contrasted with increased toxicity with the addition of retifanlimab.[15]

The most common toxicities in both study arms of the InterAAct-2 trial were hematologic, with anemia (66% versus 70%), neutropenia (47% versus 44%), and thrombocytopenia (14% versus 20%), in the retifanlimab and placebo arms, respectively. In the experimental arm, there were 83% grade ≥3 adverse events as compared to 75% in the placebo arm, with 4 versus 1 treatment-related deaths.[15] Of note, the discrepancy in serious adverse event rates and treatment-related adverse events appears to be mediated by the immune-related adverse event (irAE) rate (49% versus 26%), which was, as expected, higher in the retifanlimab arm.[15] These adverse events led to an 11% treatment discontinuation rate versus 3% for chemotherapy alone.[15] However, the most common irAEs were reported to be grade 1 or 2 in severity and did not typically lead to dose interruptions, delays, or discontinuation, and included neuropathy (11%), hypothyroidism (14%), diarrhea (10%), hyperthyroidism (8%), pruritis (7%), adrenal insufficiency (5%), and rash (2%).[15]

Despite the irAEs highlighted above, most treatment delays were due to hematologic toxicities, owing to the carboplatin and paclitaxel backbone.[15] The dosing regimen for this protocol is carboplatin AUC 5 on day 1 and paclitaxel 80 mg/m^2 on day 1, 8, and 15 of a 28-day cycle, for up to 6 cycles.[16] However, dose-density can lead to treatment interruptions due to cumulative hematologic toxicities.[15] No prospective trials have compared alternate dosing schedules in this setting, and almost all prospective ASCC trials use the weekly paclitaxel regimen. However, there are small retrospective single-institution data that support the use of carboplatin AUC 5 and paclitaxel 175 mg/m^2 every 3 weeks. One such study by Kim *et al*. included 12 patients with first-line metastatic ASCC and 6 patients with locally advanced and/or pretreated ASCC, from a single-centre tumour registry, and identified an ORR of 53%, including 3 pathologic complete responses, with a median OS of 12.2 months.[16] Data from other cancer types suggest that 3-weekly dosing is less likely to cause treatment delays due to anemia than the dose-dense version, at the expense of potentially increased neuropathy or neutropenia.[16,17] Therefore, for patients with significant anemia leading to treatment delays, alternate dosing (dose reductions or schedule adjustments) of carboplatin and paclitaxel may be beneficial and attempted at the discretion of the treating oncologist.

Overall, despite the added toxicities, OS benefit was generally in favour of the addition of retifanlimab across all predefined subgroups, aside from patients with PD-L1 expression <1%, and those who are HIV-positive, aged ≥75 years, and with locally recurrent disease.[15] It must be acknowledged that, given the small numbers of patients in each of these subgroups (and resultant wide confidence intervals), these data should be interpreted with caution and should not form the basis of treatment allocation decisions and eligibility for retifanlimab. Taken together, the InterAAct-2 trial has established the combination of carboplatin plus paclitaxel with retifanlimab as the preferred first-line standard of care for recurrent or metastatic ASCC. Indeed, this regimen is currently approved by the US Food and Drug Administration (FDA) for this indication. However, at the time of writing, retifanlimab in combination with carboplatin and paclitaxel is pending reimbursement review by

Canada's Drug Agency. Additionally, several larger immunotherapy trials are ongoing for advanced ASCC or mASCC, examining alternative chemotherapy and immunotherapy regimens. Notably, the field is awaiting results from the EA2176 trial, a phase III trial of carboplatin plus paclitaxel with nivolumab (anti-PD-1) in mASCC with PFS as primary endpoint and OS, ORR, and toxicity profile as secondary outcomes in a 2:1 randomization. Further, the SPARTANA trial is evaluating the feasibility of spartalizumab (anti-PD-1) in combination with a docetaxel, cisplatin, 5-FU (DCF) chemotherapy backbone, alongside radiation, to enhance tumour antigen shedding and anti-tumour immune activation.[18,19] These studies may provide feasible alternatives, or improvements, to the current standard of care.

Second-line and/or Platinum-Refractory Therapy

While carboplatin plus paclitaxel with or without retifanlimab remains the most frequently used first-line regimen, there is no established standard of care in the second-line setting, for which cytotoxic chemotherapy, immunotherapy, or participation in clinical trials may be considered. Despite a current lack of large prospective second-line trials for advanced ASCC, likely reflecting disease rarity and the need for a logistically onerous global initiative to enroll sufficient numbers of patients, there are multiple options with established ORRs ranging from 10%-30%, PFS of 2-3 months, and OS estimates of 10-20 months. Treatment decisions need to be individualized in this data-limited space, taking comorbidities, performance status, and patient preferences into consideration. Since chemotherapy trials have been extensively reviewed in other publications, we will summarize key recent IO trials below.[20]

The phase II POD1UM-202 trial assigned 94 previously treated patients with advanced or metastatic ASCC, who were either intolerant of, or progresses following, platinum-based chemotherapy, to receive retifanlimab in the second-line setting.[21] The study reported an ORR of 13.8% (95% CI, 7.6-22.5), with an 1.1% complete response rate, 12.8% partial response rate, and a stable disease rate of 35.1%, resulting in a disease-control rate of 48.9% (95% CI, 38.5-59.5).[21] Median PFS and OS were 2.3 (95% CI, 1.9-3.6) and 10.1 (95% CI, 7.9-not estimable) months, respectively.[21] Safety signals were consistent with prior IO trials. Likewise, the phase II KEYNOTE-158 basket trial evaluated pembrolizumab (anti-PD-1) monotherapy in multiple tumour types.[22] The anal cancer cohort of 112 patients revealed an ORR of 15% (95% CI, 8-25) in PD-L1-positive tumours and 3% (95% CI, 0-17) in PD-L1-negative tumours. The median OS was 11.9 months (95% CI, 9.1-14.9), with a PFS of 2.0 months (95% CI, 2.0-2.1), and the median DOR was not reached at the time of published analysis.[22] Of note, no definitive conclusions could be drawn based on PD-L1 status based on the recorded number of events.[22] Lastly, a 2017 multicentre, single-arm, phase II study investigated nivolumab monotherapy for treatment-refractory mASCC with ORR as the primary endpoint.[23] Of the 37 enrolled patients, 9 (24%) exhibited a therapy response, including 2 complete responses and 7 partial responses.[23] Taken together, these studies suggest a modest benefit for single-agent IO in terms of ORR, OS, and PFS, with a subset of patients (yet to be defined) exhibiting longer-term disease control. Single-agent IO in second- and later-line settings, therefore, represents a modest tool in the limited armamentarium of treatment options and is associated with a relatively favourable risk-benefit ratio. To our knowledge, no jurisdiction in Canada reimburses IO in the refractory setting of advanced ASCC.

Based on evidence from other cancer types, IO treatment intensification has also been assessed in mASCC. The phase II NCI9673 trial part B investigated nivolumab with or without cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibition using ipilimumab in patients with refractory mASCC.[24] The addition of ipilimumab to nivolumab did not improve PFS (2.9 months [90% CI, 1.9-3.8] versus 3.7 months [90% CI, 2.0-5.6]), exhibited similar ORR (17.4% versus 21.5%; p=0.89), and OS (20.0 months versus 15.9 months; p=0.89) compared to nivolumab monotherapy.[24] Further, dual ICI use resulted in significantly higher rates of grade ≥3 adverse events (25% versus 12%), highlighting the need for caution regarding combination ICI treatments in this setting.[24]

Taken together, while there is presently no universally accepted second-line standard of care in mASCC, treatment must be individualized with options including cytotoxic chemotherapy (i.e., folinic acid, fluorouracil, plus oxaliplatin [FOLFOX]; folinic acid, fluorouracil, plus irinotecan [FOLFIRI]; cisplatin plus 5-FU; cisplatin plus mitomycin-c; or single-agent taxanes) or single-agent IO (if

accessible). Enrollment in clinical trials is highly encouraged, recognizing that trials in this setting require global recruitment.

Novel or Emerging Therapeutic Options

For patients who have progressed on the abovementioned lines of therapy, contemporary clinical research has explored several novel treatment combinations including epigenetic agents, vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibition, bispecific immunotherapies, and novel anti-PD-1 agents.[24-30] In this setting, ORRs of 10-30%, PFS of 4-6 months, and OS of 12-18 months have been achieved in small prospective phase II studies.

For example, the phase II open-label, non-randomized, multicentre basket trial PEVOsq assessed pembrolizumab and vorinostat, a histone deacetylase (HDAC) inhibitor, in a mixed cohort of recurrent or metastatic SCC, including 29 patients with mASCC.[25] The combination therapy resulted in an ORR of 31%, with a mOS of 18.8 and mPFS of 5.8 months.[25] Further, a phase II trial of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) in 20 previously IO treatment-naïve patients revealed an ORR of 10%, PFS of 4.1 months (95% CI, 2.6 - NA), and mOS of 11.6 months (95% CI, 9.5-20).[26] Other early-phase drug trials in this space have evaluated avelumab (anti-PD-L1), avelumab plus cetuximab (anti-EGFR), atezolizumab plus bevacizumab, bintrafusp alfa (PD-L1 and TGF-β blocking bispecific fusion protein), and other PD-L1 inhibitor combinations with ORRs ranging from 11%-31%.[26-30]

EGFR-targeted therapies have also been trialed due to similarities to cervical and head and neck tumours in terms of histology, radiosensitivity of early-stage disease, and biologically HPV-associated disease.[30] These cancers (cervical and head and neck) likewise overexpress EGFR, and in a cohort of 101 patients 90% were positive for EGFR by IHC. Further, EGFR-targeted treatment resistance mechanisms involving downstream effector (*KRAS* and *BRAF*) mutations are less common than in other cancers.[30] Based on this, anti-EGFR treatment with cetuximab was assessed in a series of heavily pretreated patients in combination with irinotecan. A response was observed in 5 of 7 patients, with a median PFS of 6 months. Although promising, this treatment has not yet been investigated in a larger phase II trial.[30]

Conclusions

While recent advances in systemic treatment options have improved outcomes for patients with advanced or metastatic ASCC, treatment in this context represents an as-of-yet unmet need in the management of solid tumours. The addition of IO to a chemotherapy backbone in the phase III POD1UM-303/InterAAct-2 trial has established retifanlimab and carboplatin plus paclitaxel as the standard of care for advanced or metastatic ASCC with improved PFS and OS (although survival results remain immature). For ICI-ineligible patients, the InterAAct trial established carboplatin plus paclitaxel as another standard of care. In the second-line setting, options include single-agent IO, chemotherapy, and clinical trials, depending on prior lines of treatment, patient performance status, and underlying comorbidities. Current biology-informed studies are examining combination regimens that include HDAC inhibitors, EGFR-targeted therapies, and VEGF-targeted therapies. Ongoing global efforts are necessary to advance the science and management of this challenging disease.

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