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This Issue of the AHNS Journal Club has been compiled and reviewed by members of the
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Dear Colleagues,

The AHNS ***Cutaneous Section*** is pleased to present the issue of the AHNS Journal Club.

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Merkel cell carcinoma: a forty-year experience at the Peter MacCallum Cancer Centre

Annie J Wang, Brendan McCann, William C L Soon, Paolo B De Ieso, Mathias Bressel, Andrew Hui, Margaret Chua, David L Kok

From the **BMC Cancer.** *January 2023.*

Background: Merkel cell carcinoma (MCC) is a rare but highly aggressive neuroendocrine skin malignancy, with Australia having the highest reported incidence in the world. There is currently a lack of consensus regarding optimal management of this disease.

Methods: This was a retrospective audit conducted by reviewing existing medical records of MCC patients presenting to the Peter MacCallum Cancer Centre (PMCC) between 1980 and 2018. The primary endpoint was locoregional recurrence. The secondary endpoints were distant recurrence, disease-free survival (DFS) and overall survival (OS).

Results: A total of 533 patients were identified. Locoregional recurrence occurring at one, two and 5 years was 24, 31 and 32%, respectively. The estimated 5-year OS and DFS were 46% (95% Confidence Interval [CI] 41-51%) and 34% (95% CI 30-39%) respectively. Older age at diagnosis (hazard ratio [HR] per year = 1.07, 95% CI 1.06-1.07, $p < 0.001$), and larger primary tumour diameter (HR =1.16, 95% CI 1.03-1.31, $p = 0.019$) were associated with worse OS on multivariable analysis. Positive or negative histopathological margin status was not associated with OS or DFS differences in patients treated with post-operative radiotherapy.

Conclusions: In our study, about a third of patients developed locoregional recurrence, distal recurrence or both, and there appears to be no change over the last four decades. If treated with adjuvant radiotherapy, there is no difference in OS or DFS with positive surgical margins. Findings should influence future guidelines.

Summary Statement

- This is the largest study to date of patients with Merkel Cell Carcinoma (MCC) treated at a single institution. This study includes 533 patients treated at a quaternary referral center over four decades with a median follow up of 64 months.
- Findings similar to other studies including that MCC is a disease of the elderly, occurs most commonly in the head and neck and prognosis is negatively influenced by increased tumor size and stage at presentation. Use of sentinel lymph node biopsy was found to be useful in upstaging patients and the increasing use of PET scan found more radiologically diagnosed nodal disease.
- This study presents useful data on optimal surgical approach for stage I-II MCC. They found no difference in overall or disease-free survival between patients who had positive or negative histopathological margins and received post-operative RT. This data potentially advocates for smaller surgical margins without an emphasis on pursuing clear margins in patients planned for post-operative RT.

Strengths

- This is the largest study to date of MCC patients treated at a single institution. The single institution nature of the study has advantages including relative uniformity of record keeping as well as having a highly protocol driven approach to the diagnosis and management of disease.
- The relatively large number of patients included in this study for this rare disease.

Weaknesses

- As this study is a retrospective chart review, there is inherent bias relating to quality of medical records kept and potentially missing data.
- The 40-year time period of the study also fell over 7 different AJCC staging systems and while all patients were classified based on current AJCC 8 staging system, this comes with a risk of stage migration. There is likely also a potential underestimation of clinical outcomes of patients treated in the modern era due to improved treatment techniques that developed over the 40-year period of the study.

Cutaneous Squamous Cell Carcinoma in Immunocompromised Patients-A Comparison between Different Immunomodulating Conditions

Ofir Zavdy, Tara Coreanu, Dvir Yohai Bar-On, Amit Ritter, Gideon Bachar, Thomas Shpitzer, Noga Kurman, Muhammad Mansour, Dean Ad-El, Uri Rozovski, Gilad Itchaki, Shany Sherman, Limor Azulay-Gitter, Aviram Mizrachi

From the **Cancers.** *March 2023.*

Background: Immunosuppression is strongly associated with an increased risk of developing cutaneous squamous cell carcinoma (cSCC). Studies on solid organ transplant recipients (SOTR) and chronic lymphocytic leukemia (CLL) patients have already demonstrated higher rates of aggressive cSCC tumors in these populations compared to immunocompetent controls. Studies on other immunosuppressed patient groups are scarce. This study was aimed at assessing the effects of different immunomodulating conditions on patients diagnosed with cSCC. We sought to compare the clinical features, treatments, and survival rates among the different study groups, as well as outcomes to those of immunocompetent controls with cSCC.

Methods: A retrospective analysis of 465 cSCC patients, both immunosuppressed (IS) and immunocompetent controls. Etiologies for immunosuppression included SOTR, CLL, chronic kidney disease (CKD), psoriasis, rheumatoid arthritis (RA) and systemic lupus erythematous (SLE).

Results:
Compared to the control group, IS patients demonstrated several significant differences. These include higher rates of positive resection margins, higher recurrence rates, and multiple SCC tumors. Patients in the IS group, who were also given immunomodulating agents, demonstrated even lower survival rates. Cox regression analysis demonstrated statistically significant decreased overall survival (OS) rates for IS patients compared to the controls (OR = 1.9, p =

0.031). SOTR patients tend to have multiple cSCC tumors (35%), with the highest number of primary tumors compared to controls (2.54 tumors per patient on average, $p < 0.001$), but also compared to all other IS groups. The average SCC lesion size in the SOTR group was the smallest, measuring at 13.5 mm, compared to the control group and all other IS groups. Decreased survival rates were seen on Cox regression analysis compared to controls (HR = 2.4, $p = 0.001$), but also to all other IS groups. CLL patients also had the highest rates of positive margins compared to controls (36% vs. 9%, $p < 0.01$) and to all other IS groups. They were also most likely to get adjuvant or definitive oncological treatments, either radiotherapy or chemotherapy, compared to controls (36% vs. 15%, $p = 0.02$) and to other IS groups. Patients in the CKD group demonstrated the highest rates for multiple cSCC (OR = 4.7, $p = 0.001$) and the worst rates of survival on Cox regression analysis (HR = 3.2, $p = 0.001$). Both rheumatoid arthritis and psoriasis patients demonstrated the shortest disease-free survival rates (2.9y ± 1.1, 2.3y ± 0.7, respectively), compared to controls (4.1y ± 2.8) and to all other IS groups.

Conclusions: Among cSCC patients, immunosuppression due to SOTR, CLL, CKD, RA, and psoriasis is associated with worse outcomes compared to controls and other IS groups. These patients should be regarded as high-risk for developing aggressive cSCC tumors. This study is the first to assess and compare cSCC outcomes among multiple IS patient groups.

Summary Statement:

- Immunosuppression is an important prognostic factor in patients with cSCC with different immunomodulating conditions affecting differently on disease recurrence and survival.
- Adverse prognostic features such as positive resection margins, PNI and ECE are more common in immunosuppressed patients.
- Solid organ recipients, patients with chronic renal failure and patients with CLL demonstrate worse outcomes and should be closely monitored when diagnosed with cSCC.

Strengths:

- Large cohort form a tertiary care center in a skin cancer endemic region.
- Long follow-up.
- Sub-analyses of different immunomodulating conditions.

Weaknesses:

- Retrospective study
- Selection bias for better management and follow-up in the immunosuppressed groups.

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Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Sapna P Patel, Megan Othus, Yuanbin Chen, G Paul Wright Jr, Kathleen J Yost, John R Hyngstrom, Siwen Hu-Lieskovan, Christopher D Lao, Leslie A Fecher, Thach-Giao Truong, Jennifer L Eisenstein, Sunandana Chandra, Jeffrey A Sosman, Kari L Kendra, Richard C Wu, Craig E Devoe, Gary B Deutsch, Aparna Hegde, Maya Khalil, Ankit Mangla, Amy M Reese, Merrick I Ross, Andrew S Poklepovic, Giao Q Phan, Adedayo A Onitilo, Demet G Yasar, Benjamin C Powers, Gary C Doolittle, Gino K In, Niels Kokot, Geoffrey T Gibney, Michael B Atkins, Montaser Shaheen, James A Warneke, Alexandra Ikeguchi, Jose E Najera, Bartosz Chmielowski, Joseph G Crompton, Justin D Floyd, Eddy Hsueh, Kim A Margolin, Warren A Chow, Kenneth F Grossmann, Eliana Dietrich, Victor G Prieto, Michael C Lowe, Elizabeth I Buchbinder, John M Kirkwood, Larissa Korde, James Moon, Elad Sharon, Vernon K Sondak, Antoni Ribas..

From **Clinical Trial - New England Journal of Medicine.** *March 2023.*

Background: Whether pembrolizumab given both before surgery (neoadjuvant therapy) and after surgery (adjuvant therapy), as compared with pembrolizumab given as adjuvant therapy alone, would increase event-free survival among patients with resectable stage III or IV melanoma is unknown.

Methods: In a phase 2 trial, we randomly assigned patients with clinically detectable, measurable stage IIIB to IVC melanoma that was amenable to surgical resection to three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant–adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group). The primary end point was event-free survival in the intention-to-treat population. Events were defined as disease progression or toxic effects that precluded surgery; the inability to resect all gross disease; disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery; recurrence of melanoma after surgery; or death from any cause. Safety was also evaluated.

Results: At a median follow-up of 14.7 months, the neoadjuvant–adjuvant group (154 patients) had significantly longer event-free survival than the adjuvant-only group (159 patients) (P = 0.004 by the log-rank test). In a landmark analysis, event-free survival at 2 years was 72% (95% confidence interval [CI], 64 to 80) in the neoadjuvant–adjuvant group and 49% (95% CI, 41 to 59) in the adjuvant-only group. The percentage of patients with treatment-related adverse events of grades 3 or higher during therapy was 12% in the neoadjuvant–adjuvant group and 14% in the adjuvant-only group.

Conclusions:
Among patients with resectable stage III or IV melanoma, event-free survival was significantly longer among those who received pembrolizumab both before and after surgery than among those who received adjuvant pembrolizumab alone. No new toxic effects were identified. (Funded by the National Cancer Institute and Merck Sharp and Dohme; S1801 ClinicalTrials.gov number, NCT03698019.)

Summary Statement:
SWOG 1801 was a multicenter phase II randomized controlled trial that compared the current standard of adjuvant pembrolizumab to neoadjuvant plus adjuvant pembrolizumab in resectable stage III and IV melanoma.

- 2-year event-free survival was 23 percentage points higher in the neoadjuvant-adjuvant cohort (72%, 95% CI 64-80) compared with the adjuvant-only cohort (49%, 95% CI 41-59), a difference that was statistically and clinically significant. This increase in event-free survival was not accompanied by an increase in the toxicity of treatment.
- Rationale for neoadjuvant pembrolizumab in patients with high risk melanoma is to sensitize pre-existing antitumor T cells when a larger disease burden exits prior to surgical excision.
- This study supports a paradigm shift in the management of patients with resectable stage III and IV melanoma from surgery first followed by adjuvant pembrolizumab to pembrolizumab first followed by surgery and then further adjuvant therapy.

Strengths:

- Large multicenter cooperative group RCT comparing neoadjuvant-adjuvant pembrolizumab to current standard of care adjuvant-only pembrolizumab.
- Demonstrates how a small change in treatment timing can have a large improvement in patient outcomes without a corresponding increase in toxicity. This study provides support to a growing body of evidence demonstrating improved outcomes with neoadjuvant immunotherapy prior to surgical resection.
- Disease response was seen across patient stages, in patients with both resectable regional and distant disease.
- Absolute differences in event-free survival outcomes between study groups are large enough (23 absolute percentage points in favor of the neoadjuvant-adjuvant arm) to be clinically meaningful and support a change in current practice, despite some of the limitations of the composite endpoint noted below.

Weakness:

- The composite endpoint of event-free survival clouds interpretation of the study results and makes communicating these results to patients challenging.
    - **Definition of event-free survival:** Event-free survival was measured from the date of randomization to the date of the first of the following endpoints: (1) disease progression or toxic treatment effects that precluded surgery, (2) the inability to resect all gross disease, (3) disease progression, surgical complications, or toxic effects of treatment that precluded the initiation of adjuvant therapy within 84 days after surgery, (4) melanoma recurrence following surgery, and (5) death from any cause.
    - **Rationale:** The rationale for choosing this endpoint was to measure the impact of the addition of neoadjuvant therapy on the ability of patients to receive standard, definitive treatment with surgery and adjuvant pembrolizumab. Given concerns that disease progression or side effects of neoadjuvant therapy could render patients ineligible for standard surgical resection and adjuvant therapy, incorporation of the reported endpoints other than RFS and OS are understandable for a phase II study.

- **Weakness of this endpoint:**
  - This composite endpoint gives equal weight to outcomes with significantly different impacts. For example, this analysis would provide equal importance to the inability to resect all disease and overall survival.
  - The study was not powered to detect differences in the individual events, meaning that interpreting the data on those outcomes that matter most to patients (recurrence-free survival (RFS) and overall survival (OS)) is limited. Furthermore, numbers of individual events other than overall survival are not provided, limiting interpretation of the data. Despite these limitations, the data are encouraging in that the survival curves continue to widen out to 36 months, a point at which events other than RFS and OS would not be expected to be impacting event-free survival. Furthermore, at the time of data cutoff, 36 deaths total had been reported, with 14 in the neoadjuvant-adjuvant group and 22 in the adjuvant-only group, appearing to favor neoadjuvant-adjuvant therapy. Future follow-up from this study will hopefully clarify the impact of this treatment change on these important outcomes.
- There was a lower rate of patients receiving definitive surgery in the neoadjuvant-adjuvant group (88%, 127 of 144) compared with the adjuvant-only group (95%, 151 of 159), most commonly due to disease progression (12 pts) on neoadjuvant therapy. The importance of this with respect to long-term disease control remains unclear until additional long-term follow-up is reported.
- The study groups were well-balanced for most factors but approached statistically significant differences in patient sex between the adjuvant-only and neoadjuvant-adjuvant arms of the study. 40% of the patients in the neoadjuvant–adjuvant group and 30% of those in the adjuvant-only group were female. This difference becomes more meaningful considering previously reported sex-based differences in tumor immune responses.
- Other factors that may limit the validity of the study include the selection of patients with primary and recurrent disease, mucosal and acral melanoma, and all locations of the body.

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Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Neil D Gross, David M Miller, Nikhil I Khushalani, Vasu Divi, Emily S Ruiz, Evan J Lipson, Friedegund Meier, Yungpo B Su, Paul L Swiecicki, Jennifer Atlas, Jessica L Geiger, Axel Hauschild, Jennifer H Choe, Brett G M Hughes, Dirk Schadendorf, Vishal A Patel, Jade Homsi, Janis M Taube, Annette M Lim, Renata Ferrarotto, Howard L Kaufman, Frank Seebach, Israel Lowy, Suk-Young Yoo, Melissa Mathias, Keilah Fenech, Hyunsil Han, Matthew G Fury, Danny Rischin DM

From **Clinical Trial - New England Journal of Medicine.** *October 2022.*

Background: In a pilot study involving patients with cutaneous squamous-cell carcinoma, a high percentage of patients had a pathological complete response with the use of two doses of neoadjuvant cemiplimab before surgery. Data from a phase 2 study are needed to confirm these findings.

Methods: We conducted a phase 2, confirmatory, multicenter, nonrandomized study to evaluate cemiplimab as neoadjuvant therapy in patients with resectable stage II, III, or IV (M0) cutaneous squamous-cell carcinoma. Patients received cemiplimab, administered at a dose of 350 mg every 3 weeks for up to four doses, before undergoing surgery with curative intent. The primary end point was a pathological complete response (the absence of viable tumor cells in the surgical specimen) on independent review at a central laboratory, with a null hypothesis that a pathological complete response would be observed in 25% of patients. Key secondary end points included a pathological major response (the presence of viable tumor cells that constitute ≤10% of the surgical specimen) on independent review, a pathological complete response and a pathological major response on investigator assessment at a local laboratory, an objective response on imaging, and adverse events.

Results: A total of 79 patients were enrolled and received neoadjuvant cemiplimab. On independent review, a pathological complete response was observed in 40 patients (51%; 95% confidence interval [CI], 39 to 62) and a pathological major response in 10 patients (13%; 95% CI, 6 to 22). These results were consistent with the pathological responses determined on investigator assessment. An objective response on imaging was observed in 54 patients (68%; 95% CI, 57 to 78). Adverse events of any grade that occurred during the study period, regardless of whether they were attributed to the study treatment, were observed in 69 patients (87%). Grade 3 or higher adverse events that occurred during the study period were observed in 14 patients (18%).

Conclusions: Neoadjuvant therapy with cemiplimab was associated with a pathological complete response in a high percentage of patients with resectable cutaneous squamous-cell carcinoma. (Funded by Regeneron Pharmaceuticals and Sanofi; ClinicalTrials.gov number, NCT04154943).

Summary Statement

- Neoadjuvant immunotherapy can be an effective treatment addition to advanced stage cutaneous squamous cell carcinoma with frequent but acceptable risk factor profile in an elderly skewed population. Three out of total 4 deaths were deemed to be most likely related to underlying cardiac disease.
- Imaging may not correlate well with degree of pathologic response. Most patients who had a pathological complete response were not classified as having a complete response on imaging.
- All 5 patients that had complete imaging response had complete pathologic response. Of the 44 patients that had partial imaging response, 30(68%) had complete pathologic response, 8(18%) had major response and 6(14%) no major response.
- Pathological responses were observed in both PD-L1–negative and PD-L1–positive patients, but the percentage of patients who had a pathological complete response was lower among PD-L1 negative patients (20%) vs PD-L1 positive patients (54%).

Strengths

- Phase 2, confirmatory, multicenter, but nonrandomized study where all patients received immunotherapy prior to surgery.
- Population favoring Stage III and IV advanced bulky disease with nodal involvement.
- Rigorous central laboratory evaluation of surgical specimens to verify pathologic response rates.

Weaknesses

- Absence of a control group; without randomization, the possibility of selection bias cannot be ruled out
- Skewed towards head and neck cutaneous squamous cell carcinoma.
- A high percentage of White male participants were enrolled.
- Relatively short median follow-up so disease-free survival after surgery are not yet available.

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