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EDITORIAL – MELANOMAS

Another Brick in the Wall: Toward a Better Understanding of Melanoma of Unknown Primary

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Melanoma of unknown primary (MUP) occurs in 1–15 % of patients with clinically detectable lymph node metastases, but as a group have not been well characterized and a number of questions remain, ranging from pathophysiology to prognosis to treatment paradigms.[1–7] In this issue of the Annals of Surgical Oncology, Gos and colleagues (reference) analyze the molecular characteristics (BRAF, NRAS, and KIT mutation analysis) of MUP in 103 patients presenting with palpable nodal metastases and treated with complete lymphadenectomy at four Central and Eastern European Cancer Centers. This relatively homogenous group of patients, evaluated over an 18 year period (1992–2010), with long follow-up (median 53 months) and not treated with BRAF or MEK inhibitors, allows us to draw insights into the behavior of a group of patients in whom the biology of disease is not well understood.

Melanoma presenting initially in a regional lymph node has been the subject of debate for many years. Initial investigators were focused on site of origin. Several hypotheses have been considered; the most commonly accepted is that these lymph nodes represented metastases from previously removed cutaneous nevi misdiagnosed as benign or from completely regressed primary cutaneous melanomas. Other theories include melanoma of primary lymphatic origin and metastases from mucosal primary sites. Unraveling the origination site of these metastatic lymph nodes proved challenging. Molecular characterization of primary melanoma of varying sites of origin has provided promise in understanding this dilemma. With recognition that mutations in BRAF, NRAS, and KIT are distinctly different between melanoma of cutaneous chronic sun-damaged skin, cutaneous nonchronic sun-damaged skin, acral sites, and mucosal primaries, the possibility of better characterizing those melanomas presenting without a primary site became possible.[8,9] The current analysis by Gos and colleagues suggests that in this large sample of patients presenting with MUP, the absence of KIT mutations, and the high cumulative incidence of BRAF (53 %) and NRAS mutations (14 %) point toward a cutaneous origin from nonchronic, sun-damaged skin as the most likely originating location of MUP.[10,11] This is consistent with other recent work characterizing the molecular expression of MUP in 44 patients (31 stage III/13 stage IV).[12] BRAF (52 %) and NRAS (24 %) had a high cumulative incidence and KIT mutations were absent. Taken in aggregate, these data sets appear to make a clear argument that stage III MUP are not of mucosal origin, but most likely of cutaneous origin from nonchronic, sun-damaged skin.

Assuming molecular characterization from several different data sets confirms a cutaneous site or origin, the next issue is whether these patients have a similar or different prognosis compared with cutaneous melanoma patients with a known primary cutaneous melanoma. Although the majority of the evidence comparing MUP to known primary stage III melanoma would favor a difference in prognosis, there is not uniform agreement.[4–6,13,14] In the five largest series to date (range of 47–262 MUP patients) comparing MUP to known primary melanoma, two found no statistically significant difference in overall survival (refs 5 and 13) and two did (refs 4 and 6). In the most recent of these (ref 14), the authors analyze three groups of patients with lymph node metastases: MUP ($n = 68$), synchronous LN metastases ($n = 111$), and metachronous LN metastases ($n = 319$). There was no difference in overall survival between MUP and patients with metachronous LN metastases, but there was a significant different between these two groups and those patients presenting

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with LN metastases at the time of initial diagnosis. In addition, the results from the South West Oncology Group S0008 trial, which randomized stage III b/c patients to interferon-alpha 2b or biochemotherapy, demonstrate an improved recurrence-free survival in 33 patients with MUP compared with those with no primaries, but no difference in overall survival.[15] The prognosis for MUP patients is not clear compared with those with known primaries. With the molecular characterization knowledge that MUP patients do appear to be of cutaneous origin, it would seem imperative to include these patients in all future adjuvant trials for stage III melanoma patients.

Although the data presented in this manuscript are a significant step in our understanding of the origins of MUP, a number of questions remain. What are the biological consequences of a completely regressed primary melanoma? Are there differences in prognosis between known and unknown primary melanoma that can be explained by differences between tumors or differences in host immune responses that also account for complete regression of the primary? Perhaps MUP patients would be very responsive to adjuvant therapy with an immunomodulator, such as ipilimumab or PD-1. Perhaps most immediately relevant: should MUP patients be included in clinical trials of patients with stage III cutaneous melanoma and are there immune-mediated differences between MUP and know primary melanoma patients that may impact response and/or toxicity to targeted agents, particularly those such as ipilimumab, where immune-mediated mechanisms are associated with both response and adverse events? Until we develop a more complete understanding of MUP, a cautious approach seems warranted. However, thoughtful clinical trial design is necessary so that patients who may significantly benefit from immunomodulator therapy in the adjuvant setting are included.

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