Has the melanoma information tsunami become a maelstrom?

John F Thompson^{*1,2} & Alexander M Menzies^{1,2}

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Since the publication of the inaugural issue of *Melanoma Management* in August 2014, intensive research efforts have seen the melanoma information tsunami gather further intensity. However, the analogy with a tsunami used in the editorial introducing that first issue [1] may no longer be appropriate, since the term applies to a wave traveling with great force in a single direction. The word ‘maelstrom’, used to describe a large and very powerful whirlpool, may now be more appropriate since there is a surging tumult of new information leading us in a number of different therapeutic directions, with several impressive secondary eddies but all circling toward a great central vortex representing cure of melanoma.

The management of melanoma in 2017 is substantially different from the management that was undertaken in 2014. Of note, the staging system for melanoma has been extensively revised, the role of completion lymph node dissection (CLND) for patients with stage III disease has been reassessed and the medical treatment of

both metastatic melanoma and high-risk early stage melanoma has changed significantly.

The American Joint Committee on Cancer 8th Edition Melanoma Staging System

To guide treatment and achieve the best possible outcome for patients with melanoma, accurate staging is of fundamental importance. It is also required to obtain reliable estimates of prognosis and to stratify patients entering clinical trials of new therapies.

In 2017, The American Joint Committee on Cancer (AJCC) published the 8th Edition of its Cancer Staging Manual [2], which contained a number of important changes to melanoma staging. The changes were based on analysis of a database of >46,000 patient records, assembled using data for patients with stage I, II and III disease diagnosed and treated at ten large melanoma treatment centers worldwide since 1988. Evidence-based changes to

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¹Melanoma Institute Australia, The University of Sydney, Sydney NSW 20160, Australia

²Sydney Medical School, The University of Sydney, Sydney NSW, Australia

*Author for correspondence: Tel.: +612 9911 7366; john.thompson@melanoma.org.au

“Systemic therapy is becoming relevant for earlier stages of melanoma...”

the melanoma tumor, node, metastasis (TNM) classification and stage grouping criteria in the AJCC 8th Edition Cancer Staging Manual included:

- Tumor thickness measurements to be recorded to the nearest 0.1 mm, not the nearest 0.01 mm;
- T1a primary tumors redefined as being <0.8 mm in Breslow thickness without ulceration and T1b tumors as 0.8–1.0 mm in Breslow thickness with or without ulceration, with mitotic rate no longer used for T substaging;
- For N categories, the terms ‘microscopic’ and ‘macroscopic’ for nodal metastases replaced by ‘clinically occult’ and ‘clinically apparent’;
- Definitions of N subcategories revised to integrate the presence or absence of microsatellites, satellites or in-transit metastases;
- Prognostic stage III groupings redefined using T-category criteria (i.e., primary tumor thickness and ulceration) as well as N category criteria;
- An additional stage III grouping (stage IIID) introduced for patients with a thick ulcerated primary (T4b) and either ≥ 4 involved nodes (N3a or N3b) or ≥ 2 involved nodes plus microsatellite, satellite or in-transit metastases (N3c);
- For each M1 subcategory, a designation added for normal or elevated LDH – (0) for not elevated and (1) for elevated – with an elevated serum lactate dehydrogenase (LDH) no longer automatically upstaging to M1c;
- A new M1d designation created for metastatic disease involving the central nervous system.

The changes in the AJCC 8th Edition are fully described and discussed in detail elsewhere, in an article by the AJCC Melanoma Expert Panel that proposed the changes [3].

Completion lymph node dissection for sentinel node-positive patients

The first multicenter selective lymphadenectomy trial (MSLT-I) [4] documented the value of sentinel node (SN) biopsy for accurate staging of melanoma patients, and a survival benefit for patients with intermediate thickness melanomas found to be SN-positive who then went on to have a CLND, compared with patients who did not have an SN biopsy but later had a therapeutic

lymph node dissection. In June 2017, the initial results of a second large international trial, MSLT-II, were published [5]. All 1939 patients in MSLT-II had a positive SN, and were randomized to CLND or observation. The results, which indicated that CLND in SN-positive patients conferred no significant survival benefit, are expected to be practice-changing, with routine CLND no longer recommended [6]. Similar results were reported in the 483 patient German DeCOG-SLT study [7].

In MSLT-II, the great majority of SN-positive patients had no additional disease identified in non-SNs when a CLND was performed, implying that the SN biopsy itself was therapeutic in most SN-positive patients with intermediate thickness melanomas (in whom a survival benefit had been demonstrated in MSLT-I). However, if CLND is not performed in SN-positive patients, the risk of node field recurrence will obviously be increased, and some patients may elect to have a CLND to minimize this risk. Additionally, patients will be deprived of the prognostic information conferred by knowledge of non-SN status, confirmed in MSLT-II to be a factor of considerable prognostic value and for this reason, CLND may still be required for patients wishing to enter adjuvant therapy trials.

Systemic therapy

Standard systemic therapy for metastatic melanoma in 2017 is with BRAF-targeted agents and checkpoint immunotherapy. While targeted therapy using combination BRAF and MEK inhibitors remains a cornerstone of treatment for patients with BRAF-mutant metastatic melanoma, the near-universal development of acquired resistance is a major problem. Although initial responses are dramatic in nearly all patients including those with brain metastases, recent long-term data demonstrate that durable disease control is achieved in very few of them [8]. There are few biomarkers that predict outcome with even modest reliability, and it has become clear that acquired resistance mechanisms are heterogeneous. Resistance involves reactivation of the MAPK pathway but efforts to inhibit this downstream at the level of ERK or to target cell cycle regulators have so far been unsuccessful. More targets are being developed but the predominant focus and major advance in the last 3 years has been the use of immunotherapy which can achieve durable survival.

The revolution in melanoma outcomes achieved with immunotherapy, initially with ipilimumab and more recently with anti-PD-1 antibodies (pembrolizumab and nivolumab), has been astounding [9–11]. There is a real possibility that cure – or at least very long term disease control – will soon be achievable in most patients with metastatic melanoma. However, further research is required to identify mechanisms of primary resistance (a long-known issue with immunotherapy) and acquired resistance (a new concept that has emerged in the last few years). Various biomarkers to predict initial response to therapy have been proposed, including baseline and on-treatment tumor, blood and gut biome markers, but those examined to date are not sufficiently robust to predict clinical outcome with accuracy [12]. Nor have biomarkers to predict toxicity been identified.

Combination CTLA-4 and PD-1 immunotherapy with ipilimumab and nivolumab is regarded by many as the current standard immunotherapy for metastatic melanoma, with a high rate of durable response, including in patients with brain metastases, but toxicity is significant. Long-term survival data are awaited to truly establish whether this is the new ‘gold standard’, and in the meantime a multitude of clinical trials involving ipilimumab and PD-1 at different dosing schedules, novel inhibitory and stimulatory T-cell checkpoint agents, other immunostimulants, combinations of immunotherapy and targeted therapy, and combinations of immunotherapy and radiotherapy are under way, all aiming to increase response rates and long-term survival but minimize toxicity.

While this maelstrom of clinical trial activity is impressive, we need to ensure that trials are designed in a way that ensures the best return on investment (for patients, clinicians and drug companies). Sequential treatments do not appear to be the best approach to achieving optimal results, but neither is combining ever more treatments in unselected patient populations. Clearly an individual, tailored approach is required, and novel drugs and clinical trial designs will undoubtedly be required to achieve the ultimate goal of complete disease control in every patient.

Advances in adjuvant systemic therapies for melanoma have also been made, so the long-running

debate about the value of high-dose adjuvant interferon is soon likely to become irrelevant. In 2016, the initial adjuvant trial of the first modern systemic therapy for melanoma, ipilimumab, demonstrated a major overall survival benefit over placebo. However while efficacy was impressive, toxicity was very high, precipitating a new debate as to whether ipilimumab is the new ‘standard’ therapy, replacing interferon (or observation) [13]. Preliminary results from a trial of adjuvant ipilimumab at a lower dose are encouraging [14], but results of trials of BRAF/MEK inhibitors and anti-PD-1 antibodies, which are more active and less toxic in the metastatic setting than ipilimumab, are eagerly awaited. It is expected that these trials will improve both recurrence-free survival and overall survival. If they do, this will represent a dramatic paradigm shift, involving the widespread use of effective and relatively nontoxic adjuvant systemic therapies for patients with stage III and resected stage IV melanoma. Furthermore, if early data from neoadjuvant trials demonstrating high response rates and durable disease control with both targeted therapies and immunotherapy are confirmed, neoadjuvant therapy may also become mainstream, as it is with many other cancer types.

Systemic therapy is becoming relevant for earlier stages of melanoma but, conversely, there has probably never been a greater role for surgery and radiotherapy in later stage disease than ever before. The interplay between surgery, systemic therapy and radiotherapy continues to evolve, but it is already clear that every melanoma patient now requires carefully integrated multidisciplinary care.

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