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State of Melanoma: An Historic Overview of a Field in Transition

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Abstract

The last 30 years has seen a revolution in the field of melanoma. Fundamental elements of the surgical, adjuvant medical, and systemic therapy of the disease have been significantly altered toward improved management and better outcomes. The intent of this article is to reflect on past efforts and research in the field of melanoma and the current landscape of treatment of melanoma. We also hope to capture the excitement currently rippling through the field and the hope for a cure. The intent of treatment for advanced melanoma which was once considered incurable, has changed from palliative to potentially curative. Outcomes from research in the fields of immunotherapy and driver mutations in the following decade will hopefully make this goal a reality.

Keywords

Melanoma; Prognosis; Biology; Immunotherapy; Targeted therapies; Neoadjuvant; Adjuvant; Ipilimumab; BRAF; MEK

“If I have seen a little further, it is by standing on the shoulders of giants.”

-Isaac Newton

Introduction

In 2014 an estimated 76,100 patients will develop new primary melanoma in the US, and 9710 will die of this disease.¹ In the US, melanoma accounts for less than 5% of all skin cancers, but is the leading cause of skin cancer mortality.² The annual rate of rise of melanoma incidence is currently estimated at 3% compared to 6% in the 70s–80 but overall mortality has been relatively stable since 1990.³ Worldwide the incidence of melanoma continues to rise and despite advances in local and systemic therapy, mortality continues to

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rise with 80% of skin cancer-related deaths attributable to melanoma.⁴ Progress in the basic molecular biology and immunology of melanoma over the past 50 years has translated into improved outcomes for patients with localized disease as well as for those with systemic disease. The distribution of the burden of disease may be seen as inversely related to the opportunities to improve outcome, with advanced disease that will be fatal less frequent than earlier *operable* disease that is the forum for adjuvant interventions, and the early *localized* disease stages most highly curable with surgery.⁵ Outcomes for patients with deeper primary lesions show a different picture. Those with deeper localized AJCC stage IIB–C have an increased risk of relapse and death, while microscopic regional stage IIIA disease detectable with sentinel lymph node mapping and biopsy have intermediate risk. Recurrent nodal disease and bulky nodal IIIB–C disease have relapse and mortality risk that approaches 70% or more at 5 years.⁵ Treatment and outcomes for advanced melanoma have improved over the past twenty years on the basis of rapid advances in the fields of tumor cell biology, immunology, and surgical techniques, radiosurgery, imaging - that are likely to further transform the field in the decade to come. This review will reflect on the progress made in the past century, and familiarize the reader with the current state and management of melanoma.

Melanoma in Antiquity

Described in antiquity as a “fatal black tumor”, the term derived from Greek (melas “dark” and “oma” tumor) was coined by Dr. Robert Carswell in 1838. References to this “fatal black tumor” can be found in the writings of the Greek physician Hippocrates in the fifth century BC while those of Rufus of Ephesus emanate from the first century AD.⁶ Hunter is credited with the first resection of melanoma in 1787. The “soft and black” mass resected from the jaw of a 35 year-old man was reported as a “cancerous fungous excrescence”.⁷ René Laennec described melanoma as a disease entity and coined the term “melanose” to describe the tumor in 1804.⁸ Dr. William Norris noted the heterogeneous appearance of the tumor and its propensity to metastasize in 1820⁹ and first noted the heritable nature of melanoma and familial atypical multiple melanoma. In further publications, he observed that most of his patients had fair skin with light colored and the futility of surgery and medical therapy in the setting of distant metastases.¹⁰ Thomas Fawcington described one of the first cases of uveal melanoma and despaired at the lack of knowledge of therapies for this “insidious” process in 1820.¹¹ In 1844, a British surgeon Samuel Cooper¹² recognized the benefit of early removal of tumor and the untreatable nature of advanced disease.

Pathogenesis

Melanocytes in the epidermis of the skin produce the pigment melanin, which occurs in several forms that variably protect the skin from ultraviolet (UV) radiation. Most melanoma is sporadic. Environmental insults followed by proto-oncogene activation coupled with suppression of tumor suppressor genes and defects in DNA repair mechanism further exacerbated by the inability of the immune system to contain these insults results in melanoma. William Norris presciently observed the hereditary nature of melanoma and light hair, and complexion associated with melanoma in 1857. He proposed that nevi and environmental exposures predispose to melanoma, observation that were validated in the

discovery of the familial atypical multiple mole melanoma FAMM syndrome^{13,14} and the sporadic dysplastic nevus syndrome.¹⁵ The connection between UV radiation exposure and increased risk of melanoma in the Australian Caucasian population was described by Henry Lancaster in 1956 whose later work demonstrated the importance of skin characteristics in the etiology of melanoma.¹⁶ These observations gave impetus to efforts to understand the genetics of melanoma. Discovery of the melanocortin receptor 1 (MC1R) on skin/hair phenotype¹⁷ and its highly polymorphic nature helped make the association between pale skin/fair hair with poor tanning response (English/Celtic Ancestry) and melanoma. Approximately 40% of familial melanomas were attributed to heritable germline mutation in cyclin dependent kinase (CDK) gene CDKN2A.¹⁸ Defects in CDK4, xeroderma pigmentosum and MC1R genes have been implicated in familial melanomas.^{19–22} Discovery of the role of the Ras oncogene family in the 1980s and their effects on downstream signaling were the first steps toward identification of driver mutations in melanoma.²³ NRAS was first identified in a melanoma cell line in 1984.²⁴ Identification of the MAPK/ERK and PI3K/AKT pathways of Melanoma tumorigenesis followed. The mutations termed 'Rapidly Accelerated Fibrosarcoma' (RAF) were initially identified in Ewings sarcoma. Systematic genetic typing identified the V600E variant to be frequent in cutaneous melanoma in 2002.²⁵ This mutation and its constitutive activation of the MAPK pathway have become the target of multiple pharmaceutical trials of small molecule inhibitors resulting in several new FDA-approved therapies. Evaluations of other histologic subtypes led to the discovery of cKIT in acral and mucosal melanomas.²⁶ Uveal melanomas exhibit driver mutations in GNAQ, GNA11 and BAP1 with low incidence of BRAF.²⁷ The differing pattern of driver mutations in different histologic subtypes of melanoma, and the numeric burden of mutations in different melanoma cell lines from single tumors and in tumor samples ex vivo^{28,29} reflect the genetic heterogeneity of melanoma and are likely to have profound implications for the molecular as well as immunological therapy of melanoma.

Risk factors

Melanoma is a disease that afflicts Caucasian Americans 20 times more commonly than African Americans. The lifetime risk of melanoma is ~ 2% (1 in 50) for Caucasians, 0.1% (1 in 1,000) for African-Americans, and 0.5% (1 in 200) for Hispanics. The risk of melanoma increases with age – and the average age at incidence is 61 but it is not uncommon among those younger than 30—and especially young women. Men have a higher lifetime risk than women. Previous history of melanoma is associated with an approximately 7% chance of developing a second primary melanoma. Exposure to UV radiation is the predominant environmental risk factor leading to melanoma. Cumulative solar exposure and sunburn events (UV-B) are both suspected as causative. UV-A exposure from tanning beds has been implicated in the risk and incidence of melanoma particularly among women under the age of 35.³⁰ This has led to the labeling of sun beds/lamps as human carcinogens by multiple health organizations including the NIH. Most melanomas arise as new lesions in the skin, although a significant fraction (25–40%) appears to arise from pre-existing nevi. The latter, clinically described as atypical³¹ and pathologically identified as dysplastic nevi³² along with congenital nevi have long been considered risk markers and non-obligate precursors

warranting surveillance. Giant congenital nevi (>20cm) carry an increased risk of melanoma and are excised when possible.³³ Family history of melanoma increases an individual's risk of melanoma up to 8 fold.^{34–37} Population based studies series have shown an increased incidence of skin cancers including melanoma in patients with CLL.³⁸ BRCA2 mutation carriers are noted to have a 2.58 times greater risk than non-carriers of developing melanoma.³⁹

Diagnosis

Patients may present with an unusual, new or changing skin lesion to their PCP or dermatologist. Melanoma can present as amelanotic flesh-colored or nodular lesions. The ABCDEs of melanoma guide decision to biopsy. American Academy of Dermatology recommends an excisional biopsy with narrow margins as the preferred biopsy technique over shave and incisional biopsy.⁴⁰ A deeper saucerization biopsy is acceptable, and incisional biopsy is appropriate for lesions suspicious for melanoma that are not suitable for excisional biopsy. If a punch biopsy is performed it should be deep enough to encompass the base of the lesion.⁴¹ Stains traditionally used to identify melanoma include a combination of S100B (in some centers this has been replaced with a pooled mixture of antibodies to Melan-A/MART1), HMB-45 and tyrosinase. Newer targets for IHC assessment include SOX10 and Mitf. Growth phase (radial vs. vertical), morphotype (nodular or superficial spreading) mitotic rate, ulceration and presence of tumor regression and tumor infiltration by lymphocytes (TIL) are conventionally reported for their prognostic implications. Melanoma can be categorized morphologically and anatomically into the uveal, cutaneous, mucosal and acral types which have differing molecular patterns of driver oncogenes. Invasive cutaneous melanomas have historically been subdivided based on growth patterns into superficial spreading (most common), nodular (next most common), and acral lentiginous mucosal and lentigo maligna morphotypes, which have differing biological behavior, prognosis, and molecular driver gene patterns.

Staging

The foundation for the current staging system was laid by the pioneering work of Wallace Clark and Alexander Breslow. In 1966, Clark proposed a system that derived from the assessment of the tissue level of invasion subsequently termed “Clark's Level” to assist in the pathological assessment of prognosis of melanoma. Invasion of the layers of skin (Clark's levels I–V representing the junction, upper papillary, full papillary, reticular and subcutaneous zones of the skin) with decreasing survival rates associated with increased level of invasion. Breslow in 1970 observed that prognosis was affected by tumor thickness and worsened with increasing thickness measured from the granular layer of the epidermis. These systems were incorporated into clinical trial structure building the framework for surgical and medical management and serving as a common language for physicians to communicate and compare patients in clinical experiences. The American Joint Committee on Cancer (AJCC) Melanoma Staging Committee has periodically reassessed the staging of melanoma for prognostic assessment and last revised the staging system in 2009 (seventh edition) which was put into practice after a period of commentary in 2010.⁵ The committee based its actions upon a multivariate analysis of approximately 38000 patients

(7,972 with Stage IV disease) from North America, Europe and Australia to revise/clarify the TNM classifications and overall stage grouping criteria. It incorporated key prognostic features including Breslow thickness, ulceration, mitotic rate for thin melanomas (replaced Clark level), involvement of lymph nodes including manifestations of lymphatic spread (satellite lesions, in-transit disease), and the presence of distant metastatic disease (lung vs. other). The system also integrated prognostic data for survival and risk of relapse within each stage. The staging system reflects excellent long term survival for AJCC stage I and II melanoma – approaching 90% and 80% respectively at 20 years whereas stage IIB and higher have an increased risk of relapse and death, with stage IIIB–C approaching 70% or higher relapse/mortality at 5 years.⁵

Prognosis

Prognosis at diagnosis is largely defined by the stage of disease. Staging incorporates clinical and pathologic features, and determines diagnostic and therapeutic pathways for a given individual. Extent of disease, including the presence or absence of lymph node involvement and any distant metastases are the most important prognostic factors. The staging system also incorporates other important prognostic ‘microstaging’ factors of the primary, such as Breslow thickness, presence or absence of ulceration, and mitotic rate of the primary tumor. Older patients have a worse prognosis regardless of the stage of disease, compared with younger patients.⁴² Among the morphotypes of melanoma, nodular melanoma, by virtue of its predominant vertical growth phase and more frequent presence of ulceration carries a worse prognosis. Acral lentiginous melanomas are more difficult to detect (inconspicuous location) and are generally first detected at more advanced stages. Lentigo maligna melanomas generally are often of longer gestation, and may be detected and operated at lesser depths of invasion. Anatomically, extremity melanomas have better outcomes than truncal or head/neck melanomas. Women tend to do better than men. Ulceration serves as marker for aggressive tumor biology and propensity to metastasize. In thin melanomas, mitotic rate ≥ 1 serves as an indication of higher risk, and therefore warrant sentinel lymph node evaluation. NRAS and BRAF mutations are also associated with differing patterns of disease aggressiveness. NRAS is associated with thicker primaries and higher mitotic rates.⁴³ These markers seem to correlate with aggressive tumor biology reflecting propensity for distant invasion.

Surgical treatment

Primary tumor

William Norris first in 1857 recognized the importance of local disease control and advocated for a wide excision of the primary tumor with surrounding unaffected tissue to prevent local recurrence.¹⁰ This recommendation formed the basis of the subsequent policy for wide local excision (WLE) which is still the standard of practice today. Its scientific basis can be found in the concept that melanoma forms discontinuous nests of tumor cells in the dermal lymphatics adjacent to the primary tumor. William Handley proposed the removal of two inches (5 cms) of surrounding tissue down to level of muscle fascia for local control⁴⁴, and margins of 5 cm were accepted until the 1990s. This hypothesis was tested in multiple large trials which looked at impact of larger margins on overall survival, local

recurrence and disease free survival.^{45–48} No benefit was associated with 3, 4 or 5cm margin in terms of local recurrence, disease free survival or overall survival. Thomas et al⁴⁹ reported the inadequacy of 1 cm compared to 3 cm WLE margins. 1 cm WLE margin arm demonstrated an increased risk of locoregional recurrence although overall survival was similar. Data from these and other trials were summarized in a metaanalysis by Haigh et al⁵⁰ showing 1 cm margins adequate for primary melanomas of 1 mm Breslow thickness but 2 cm margins preferable for 1–2 mm thickness and 2 cm margins recommended for greater than 2 mm. Margins should always be negative at time of final pathology evaluation. Mohs Micrographic Surgery (MMS) is inadequately evaluated. Generally it has been done by dermatologists who have not had facility with sentinel node biopsy—so has left patients often with margins that are hard to assess in terms of their en bloc pathological status, and lacking in the regional sentinel node assessment that has since 2000 been recommended by the AJCC and other melanoma expert groups. Moh's approach for cutaneous melanoma in general has been discouraged given the concern that this surgical technique ignores the biology of melanoma, the prognostic significance of discontinuous lymphatic spread, and is done without the capacity to verify adequate margins in that the successive layers of skin taken in this procedure are not subjected to peer reviewed pathological assessment in the manner that formal wide excision specimens conventionally may be. The fact that Moh's surgery is performed in a relatively limited number of isolated silos suggests that the lack of prospective clinical trials comparing MMS to WLE to provide more rigorous evidence-based analysis of this open question is a problem that will not soon be rectified,

Lymphadenectomy

Early on, physicians realized the aggressive nature of melanoma and its propensity for lymphatic and hematogenous metastasis—and the futility of aggressive locoregional surgery once it had spread to distant sites. Early surgery with curative intent was emphasized with the goal of local-regional control. Based on the observation that melanoma spreads predominantly initially to regional lymph nodes, Herbert Snow proposed that elective lymphadenectomy (ELND) should be included with WLE to obtain cure (1892).⁵¹ His hypothesis and the work of Dr. William Handley (1908) reflected a stochastic model of tumor dissemination in which lymph nodes served as a launching pad for distant metastases. Multiple prospective randomized clinical trials from 1972 onward showed no survival benefit from ELND^{52–54} although WHO trial 13 evaluating immediate LND (ILND) vs. delayed LND (DLND) in 240 patients with >1.5 mm thick truncal melanoma suggested benefits for patients with occult microscopic LN metastases at the time of ILND.⁵⁵ The more recent understanding of prognostic factors such as Breslow thickness, ulceration, mitotic index and their clinical application alongside technical advances in sentinel lymph node evaluation put this controversy to rest.

Lymph Node Evaluation

ELND for patients with truncal and head & neck region melanomas proved to be problematic given the ambiguous nature of lymphatic drainage associated with these regions. This technical issue spurred research into technologies to identify lymphatic drainage patterns—and Wong and Morton⁵⁶ in 1977 showed that dye and radioactive tracers injected into skin around a melanoma would allow the reliable identification of the draining

lymph node(s) and basins associated with truncal dermatomes. This novel technique – lymphoscintigraphy--allowed the development of the hypothesis that the “sentinel” lymph node could guide prognostic assessment and surgery as well as other therapies for melanoma. This hypothesis postulated that a unique LN is the first to receive lymphatic drainage from a tumor site, and therefore should also be the first for melanoma metastases. The use of vital blue dye allowed Morton and his colleagues to demonstrate that the procedure accurately identifies and allows selective biopsy of the SLN for evaluation of potential involvement by tumor metastases.⁵⁶ The use of blue dye along with radiotracer coupled with portability of radiotracer detectors vastly increased the success rate of SLN biopsy. Retrospective analysis by Gershenwald et al⁵⁷ demonstrated that SLN status was the most significant prognostic factor for disease-free and disease-specific survival in univariate and multiple covariate analyses. They also concluded that the SLN status should guide decisions regarding the pursuit of complete LND (CLND) in those patients (~20%) where the SLN was positive. There is general consensus SLN biopsy is justified for intermediate thickness melanoma of >1mm Breslow thickness, given that ~20% of these patients will have occult LN involvement.⁵⁸ Thinner melanomas have lower risk of regional and distant metastases. Decisions regarding SLN biopsy among patients with thin melanomas (<1mm) is reasonably guided by the presence of adverse prognostic factors – a mitotic rate >1/mm² or the presence of ulceration, tumor lymphocyte infiltration, or a deep margin positive in the original biopsy. Patients with thicker melanomas ≥4mm should also undergo SLN evaluation given the prognostic value of SLN involvement, and the dependence of adjuvant therapy decision-making upon accurate staging at the LN station. Also some patients may be cured with SLND especially in the setting of LN micro metastases. Positive SLN involvement is currently an indication for CLND based on the Multicenter Selective Lymphadenectomy Trial (MSLT-1).⁵⁸ The implication of MSLT-1 and subgroup analysis showing that all patients with micro metastatic disease benefit from CLND has generated debate. Even today, CLND remains a morbid procedure. A minority of patients with SLN involvement exhibit non-sentinel lymph node involvement on CLND. MSLT-I data show that 88 % of patients who have a single tumor-containing sentinel node will have no additional nodal metastases when the CLND specimen is examined. The SunBelt melanoma trial showed non-sentinel LN involvement to be approximately 16%.⁵⁹ Survival benefits were seen only on subgroup analysis of MSLT-1. An argument can be made that the biology of SLN micro-metastatic disease in the SLND group may differ from the observation group where palpable LN metastases later developed--and that these two groups can not strictly be compared. For most, the evidence that SLND yields critical prognostic information and may be associated with improved morbidity and mortality associated with bulky regional recurrence has led to the adoption of this approach. However, this debate continues, and the questions surrounding the reasonable uses and therapeutic implications of the SLN are further being pursued in the MSLT-II trial that is ongoing. This study will randomize patients with positive LNs to either ILND or observation, with CLND reserved for patients with confirmed non sentinel node metastases.⁶⁰ It will also help answer the question whether SLN biopsy in some patients is both diagnostic and therapeutic. The importance of the immunobiology of melanoma at the regional lymph node cannot be understated—and studies now in progress at our center and others across the world are addressing the molecular profile of the SLN, which may guide prognosis and future treatment of disease in

a more refined manner. These studies are asking questions beyond whether there is tumor in the SLN, or not—such as whether the SLN host response is adequate or dysfunctional as it now appears it may be in a significant fraction of patients. The SLN as a forum for biological study, and as a pivot point for tumor progression, is likely to be a productive focus of studies upon the immunobiology of this disease for years to come.

Medical Management

The vast majority of patients present with early stages of diseases, so skin examination for early detection is a mandate for all physicians in primary care, as well as those who specialize in the management of melanoma from medical, as well as surgical and dermatological disciplines. Data from Germany, where the state of Schleswig Holstein adopted a program of screening amongst dermatologists, and many primary care practitioners now suggests that routine full body skin examination significantly reduces the incident thickness of melanoma and the mortality attributable to the disease by up to 50%, based upon time trends for melanoma incidence and mortality in the state of Schleswig Holstein compared to surrounding German states, and neighboring Denmark. These results have already led to the nationwide pursuit of regular skin screening for detection of melanoma across Germany—and health care systems elsewhere in the world are considering the role of screening and secondary prevention on this basis.⁶¹ Whereas the German model utilized a day-long training module simpler internet-based training modules that require only 1–2 hours for primary care physicians⁶² may provide more practicable current alternatives, and one such primary care educational effort coupled with recommended annual total body skin screening has been initiated in the UPMC Health System, where incident melanoma thickness and melanoma mortality will be followed closely over the next several years. These measures, together with evidence that appropriate surgical management cures most patients with stage IA–IB melanoma, and many with stage IIA disease, are rapidly evolving at this time. Overall 5 year survival rates for early stage disease (AJCC IA–IIA) exceed 80%.⁵ The pattern of relapse for operable early melanoma suggests that data for such patients should be judged at longer horizons. The insidious nature of some melanoma relapses, and the later distribution of relapses from early-stage disease make the issues of surveillance of relapse particularly important.⁶³ There are wide variations in the recommended frequency, and the utilization of radiological and biomarker studies across the world. These lie beyond the scope of this overview, except to note that the economic and patient anxiety and overdiagnosis toll of surveillance have not always been factored into recommendations (e.g. S3 German, Italian, and other high-intensity programs as compared with Australian, Dutch, British and more minimalist recommendations). Sadly, there is little rigorous evidence to support the application of interval radiological or biomarker studies in the follow-up of melanoma patients. Closer interval follow-ups utilizing imaging and blood testing for biomarkers such as S1000B, which have been favored in Europe have not been demonstrated to translate into improved survival outcomes when compared to clinical assessment at wider intervals. The data that are available generally do not account for the enormous fiscal costs and potential for patient and societal harms of the imaging assessments proposed. Since therapies for advanced melanoma are improving rapidly, the data upon surveillance for earlier cohorts of patients will not be applicable to the present and

future in which therapies may have increased potential for cure of the disease in the adjuvant, as well as the metastatic settings. The need to develop evidence-based approaches to surveillance of low-, intermediate-, and high-risk patients (stage IA–B, IIA–IIIA, and IIIB–C and other resectable disease) are pressing. Evidence that would guide us in regard to which patients are at risk of late relapse is critical to determine which patients are reasonable to consider for surveillance, and ultimately, for adjuvant therapy. The role of medical therapy in reducing the risk of relapse after surgery i.e. adjuvant therapy has been compartmentalized in relation to low-, intermediate-, and high-risk populations of patients, with variable results. Research using more informative tissue assessment is ongoing to determine the efficacy of ‘neoadjuvant’ therapy in melanoma. Agents in use today have fulfilled some of the criteria that Paul Ehrlich (1854–1915) articulated more than a century ago—for the “*magische Kugel*” or magic bullet –and these will likely change our approach to surveillance for recurrence in intermediate and high risk operable disease, as well as inoperable disease, as therapies that can cure metastatic disease become more generally available.

Immunology and Immunotherapy in Melanoma

Burnet et al. coined the term ‘immune surveillance’, which implied surveillance of the host for malignant cells, which were presumed to be recognized and destroyed as they emerged. This idea was supported by the observation of spontaneous regression in human melanoma, the lymphocytic/dendritic infiltrates documented pathologically in and around primary melanoma tumors, and the increased incidence of melanoma among immunosuppressed patients. The regression of melanoma among recipients of blood transfusions where the blood was derived from patients with history of melanoma regression⁶⁴ and the presence of tumor-specific T cells and antibodies in patients as demonstrated by Morton et al^{65,66} showed the importance of immunology in melanoma pathogenesis. Golub et al⁶⁷ were able to demonstrate *in vitro* increased cytotoxic activity of melanoma patient derived lymphocytes against melanoma cell lines. Mouse models showed the feasibility and efficacy of adoptive lymphocyte transfusion.⁶⁸ The discovery of Interleukin 2 (IL-2) as a T cell growth factor helped pave the way for *in vivo* studies of immune modulation, and its role in advanced melanoma. These observations and studies form the bed rock of vaccine studies, high dose IL-2 cytokine, interferon α 2b (IFN α 2b), anti-CTLA4 cytotoxic T lymphocyte-antigen 4 blocking (ipilimumab, tremelimumab) and anti PD-1 (Programmed Death 1) therapies that will be discussed as they have revolutionized melanoma therapy (please see later discussion).

Adjuvant treatment

The goal of adjuvant therapy is to reduce the risk of relapse for patients by treatment at a time when measurable or gross disease is undetectable following surgery. This therapy has been pursued in melanoma as in other solid tumors to target potential micro metastases after the patient has been surgically rendered disease-free. Given the evidence of the immunogenicity of melanoma, adjuvant therapy has been pursued with each of the successive generations of immunomodulators that has been developed over the past 50 years, beginning with bacterial immunostimulants like BCG and *C. parvum*. The wider availability of interferons, first as nonrecombinant crude material purchased from the

Finnish Red Cross by the American Cancer Society^{69–71} was followed by the industrial production of recombinant IFN by multiple pharmaceutical firms, and the first systematic dose-response evaluations by multiple routes for advanced and then adjuvant settings of disease. IFN α 2b was evaluated in a Phase I–II study in patients with metastatic melanoma and other cancers by Kirkwood et al⁷⁰. Results showed response rates (RR) comparable to single agent chemotherapy and durable responses in one third of patients who responded. Phase III trials commenced in the 1980s and 90s evaluating the role of adjuvant IFN α 2b in various doses and schedules for patients with resectable deep primary and regional nodal involvement by melanoma. Based on the results of a series of studies of the Eastern Cooperative Oncology Group (ECOG) beginning in 1984, the FDA in 1995 approved high dose IFN α 2b (HDI) for the adjuvant treatment of stage IIB and stage III melanomas. This randomized multicenter phase III study showed benefits in terms of overall survival (OS) and disease free survival (DFS) compared to observation. Low dose IFN α 2b and intermediate dose IFN α 2b were then evaluated in multiple French, Austrian and European cooperative group trials - WHO Melanoma Programs trial 16, EORTC 18871, 18952, 18991 (pegylated IFN α 2b), and Nordic Melanoma Cooperative Group trials where relapse free survival (RFS) benefit was consistently observed. A recent collective meta-analysis⁷² concluded that across all dosages, RFS benefit is observed with an HR ~0.83 and OS HR ~0.91. Analyses of individual trials has shown OS benefits only with HDI as reported in the E1694 and US Intergroup trial E1694, which evaluated HDI in relation to a vaccine that is now known to have had no significant effect upon either RFS or OS.^{72–74} Debate continues regarding the effects of alternative regimens in retrospectively identified populations such as those with ulcerated primary tumors and microscopic nodal disease, where current trials are prospectively testing the effects of alternative regimes of PegIFN. FDA based the approval of HDI, originally given for one year-upon mature 7-year data from E1684. In 2011 FDA approved the 5 year treatment regimen of PegIFN on data from EORTC 18991 showing overall significant RFS improvement at an early median follow-up of 3.8 years. However, a subsequent more mature analysis at 7.6 years median follow-up for the pegIFN α 2b has shown a lesser RFS benefit with HR 0.87, which on ITT analysis is of marginal significance. As there has never been any evidence of OS impact for this regimen, the status of this agent is less clear than that for the original E1684 HDI regimen. The historic observations of early improvement of outcomes with HDI led to a series of studies testing 1 month of therapy vs. 1 year, or 1 month of therapy vs. observation—but these now⁷⁵ have been rigorously tested, and demonstrate no evidence of durable benefit from 1 month alone, so that this chapter of investigation has been closed. Flaherty et al. have conducted the intergroup trial S0008 testing biochemotherapy vs. HDI, and have shown a significant RFS benefit of BCT over HDI for the first time in history—but without any evidence of an impact upon OS. These findings may not be revisited given the rapid advances in molecularly targeted therapy of the tumor with BRAF, MEK, and possibly ERK inhibitors that have entered adjuvant exploration with results pending, and the advances in immunotherapy with immune checkpoint inhibitors such as anti-CTLA4 blocking antibodies, and anti-PD 1 and anti-PD L1. Current clinical trials evaluating the role of ipilimumab in the adjuvant setting are enrolling across the US Intergroup, and likely to complete accrual by 2014. These will evaluate the RFS and OS impact of ipilimumab at 3 or 10 mg/kg in relation to the standard

of HDI, in more than 1500 patients from ECOG-ACRIN and SWOG, as well as other US Cooperative Groups and the NCI-Canada, and ICORG.

Neoadjuvant Treatment

Neoadjuvant therapy in multiple solid tumors (breast, bladder, esophageal and bladder) is associated with better outcomes in terms of survival and surgical outcomes. Given the evidence of immunogenicity and the phenomenon of immune evasion with progression in melanoma, the use of immunomodulatory agents for the neoadjuvant setting has been attractive for the past decade. Phase II trials have evaluated chemotherapy in combination and with immune modulatory agents (Biochemotherapy –BCT) including such agents as IL-2, IFN α 2b, cisplatin, dacarbazine, vinblastine. As might be expected, these trials showed a higher RR but were associated with significant toxicities.^{76,77} Phase III studies evaluating BCT vs. polychemotherapy showed no benefit in terms of response rates or progression free survival.^{78,79}

The use of the neoadjuvant platform to investigate mechanisms of action, beyond the response of disease in this earlier setting of potential resectability was first reported from studies at the UPCI in 2006 by Moschos et al.⁸⁰ Patients (n=20) received IV daily IFN as in the first month of the one-year E1684 regimen, followed by surgery with the goal of evaluating both response and tissue correlates of therapy. Ten percent of patients (n=2) demonstrated pathologic CR and 40% (n=8) had PRs. Tumor specimens systematically evaluated prior to and following therapy showed increased T cell and dendritic cell (DC) populations with radical changes in the level of constitutively expressed STAT3 in the tumor tissue over the month of IV IFN. The same approach undertaken at UPCI with ipilimumab showed increased tumor infiltration by activated T cells with induction/potential of memory T cells. The change in Treg observed within the tumor showed an inverse relationship with clinical benefit and was associated with improved PFS at one year.⁸¹ Study of the combination of ipilimumab and IFN is now ongoing in the neoadjuvant setting at UPCI to pave the way for this combination in future phase III trials.

Management of Metastatic Inoperable (Advanced, Systemic) Disease

The helplessness felt by Dr. Thomas Fawcington in 1826 at the lack of therapies available for patients with metastatic has been shared by medical specialists with an interest in melanoma to the present. However, advances in the field of metastatic melanoma have changed in the past few years in ways that few in the field could have predicted a decade ago. These notwithstanding, melanoma is still a disease that is incurable for a majority of patients. For the 40% of patients with mutated BRAF V600E who have responded and then relapsed (or less often failed altogether to respond) with molecularly targeted therapies including the BRAF and MEK inhibitors, disease progression is often rapid and options remain palliative in nature. The results with the currently approved immunotherapies IL-2 and ipilimumab benefit 15–20% of patients and may be prolonged—but do not benefit a majority of patients. While the results of the anti-PD1 checkpoint inhibitors have been gratifying and durable in a somewhat larger fraction of patients, these are at best half the population, and as yet have not received regulatory approval.

Most common sites of distant spread include the lung, liver, bone and brain (majority asymptomatic). Local recurrence can range from 1% to 12% for melanomas in thickness 1mm to 3mm respectively.⁸² Melanoma, like hormone receptor ER/PR+ breast cancer, renal cell carcinoma, and low grade lymphomas, presents not infrequently as a late hematogenous relapse. Surgical resection to render patients disease-free should be explored for patients with solitary or limited metastasis, in a multidisciplinary setting. In trials, patients undergoing metastectomy in the setting of long prior DFS and oligometastatic disease showed that up to 40% 5 year DFS.^{83,84} Local recurrence is treated with resection for negative margins. Medical treatment for melanoma over the past thirty years has evolved from single agent cytotoxic chemotherapy to immunotherapy and to tailored signaling inhibitor ‘molecularly targeted’ anti-tumor agents that in many ways fulfill the proverbial hope for a “magic bullet”. This coming revolution is likely to be even more paradigm-shifting as regards the immunotherapy and checkpoint inhibitors like anti-CTLA4, and anti-PD1 or PDL1—and will be overviewed here and then detailed in balance of this volume.

Chemotherapy

The origins of chemotherapy for cancer lie in the World War I exposure of soldiers to mustard gas, which was the precursor of the therapeutic mustard alkylators and nitrosoureas such as BCNU. Unfortunately these agents remain toxic and their efficacy has been marginal in melanoma, although dacarbazine was approved as a nonclassical alkylator and remains on the formulary, and oral analogues such as temozolomide have been approved for therapy of other solid tumors and have had a role in melanoma over the past generation. Dacarbazine (DTIC^R) was approved by the FDA in 1975. Studies in the 1970s^{85–87} showed response rates of 19–28% and OS of ~5 months but larger recent studies suggest response rates of ~10%.⁸⁸ Temozolomide (TMZ), an oral progenitor of the active agent of dacarbazine, has demonstrable CNS penetration but only small gains over dacarbazine. Melphalan was systemically used in 60s for melanoma⁸⁹ but today is only utilized in isolated limb infusion or perfusion therapy for patients with extensive *in transit* disease of the extremity.⁹⁰ Platin agents such as cisplatin (RR 16.3%)⁹¹ and carboplatin (RR 19%)⁹² have not shown superiority to dacarbazine. Vinca alkaloids including vindesine, vinorelbine and vinflunine were explored again without significant benefit over dacarbazine. Nitrosoureas and particularly fotemustine and lomustine have been explored on the basis of their lipophilic nature—but the hopes that these agents would prove useful for brain metastases have not been substantiated. The taxanes, including paclitaxel (RR 15.6–16.4%)^{93,94} and docetaxel (RR=17%)⁹⁵ have been explored, and the first benefit over dacarbazine has been reported by Nab-Paclitaxel in a phase III study.⁹⁶ Progression-free survival, the primary endpoint, was significantly improved, with nab-paclitaxel (median 4.8 versus 2.5 months, HR 0.79, 95% CI 0.63–0.99). There was a trend toward improved overall survival—median 12.8 versus 10.7 months (HR 0.83, 95% CI 0.58–1.20, *p* = 0.09). Combination chemotherapy has not shown superiority to single agent dacarbazine, and commonly used/ compared regimens included cisplatin, vinblastine, dacarbazine (CVD) or cisplatin, tamoxifen, carmustine, dacarbazine (DBCT or Dartmouth regimen). CVD was compared to dacarbazine in a phase III study where RR was 19% vs. 14% respectively without a difference in survival. In phase III, DBCT was found not superior to dacarbazine, with RR of 18.5% vs. 10.2% respectively and no difference in OS.⁹⁷

Biochemotherapy (BCT)

BCT arose from the effort to achieve durable responses using immunotherapy coupled with the rapidity and magnitude of responses obtained using chemotherapy. Chemotherapy combined with IL-2 and/or IFN α 2b have been tested in multiple phase I, II and III studies. Addition of IFN α 2b to single agent chemotherapy^{98–100} or multi-agent chemotherapy^{101–103} did not show additional durable benefits despite high overall RR (up to 50%). Similarly IL-2 did not show benefits added to chemotherapy.^{104–106} In an effort to gain the synergistic effects of IFN α 2b and IL-2, the combination was added to CVD in both sequential and concurrent dosing. Both approaches resulted in high ORR with 23% CR and 9% durable response.¹⁰⁷ CVD with IFN α 2b and IL-2 given concurrently was compared to CVD alone in a phase III study. No clear superiority was discerned between the two arms in terms of ORR and OS.⁷⁸ Dartmouth regimen with IFN α 2b and IL-2 compared to DBCT again showed no difference in terms of OS or PFS.¹⁰⁸ Although BCT regimens produced high response rates, this did not translate into survival benefit with the added expense of patient toxicity and inconvenience given complex delivery schedules in spite of attempts to deliver cytokines subcutaneously.

Immunotherapy

The goal of immunotherapy has been to activate the immune system, to recognize and kill tumor cells, with the thought that where cytotoxics had first order kinetics and could not be hoped to eliminate the last tumor cells, whereas immune approaches might attain this goal. Immune agents currently approved for treatment of metastatic melanoma include high dose IL-2 (HD-IL-2) and Ipilimumab. IL-2 was the second cytokine to show significant antitumor activity in patients with metastatic melanoma after IFN α 2b in the adjuvant setting. Efforts at the NCI^{109–111} demonstrated the effects of IL-2 on T cells and the induction of lymphocyte-activated killer cell (LAK) function, which was associated with cellular tumoricidal functions *in vitro*. This effect was noted to dose-dependent. Phase II clinical trials of IL-2 as a single agent alone or in combination with LAK cells (adoptive cell therapy) were conducted in the late 1980s and early 90s.^{112–114} Data from these trials (n=270 patients) showed an overall objective response rate of 16% with 17 complete responses (CR=6%) and 26 partial responses (PR=10%).¹¹³ Durable responses in these phase II trials were taken to regulatory review with FDA approval of IL-2 in 1998. Lower doses of IL-2 given subcutaneously alone or in combination with other immunotherapies did not show superiority to HD-IL-2.^{115,116} Similarly, other cytokines including IL-12, IL-18 and granulocyte macrophage colony stimulating factors did not show superiority to IL-2.¹¹² A relatively small phase III study (n=182) combining IL-2 with gp100 peptide vaccine compared to IL-2 showed promise. The combination arm showed greater CR (16% vs. 6%) with increased median OS (17.8 vs. 11.1 months; P=0.06).¹¹⁷ IL-2 in combination with Ipilimumab and anti PD-1 antibody remains a topic of interest given the perceived synergies between these therapies.

Up-regulating the host immune response to achieve therapeutic antitumor responses in melanoma has become a reality in relation to the effector T cell response to melanoma. Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) is an inhibitory immune checkpoint which down-regulates T-cell proliferation. Antibody blockade of CTLA-4 leads to T cell

proliferation and IL-2 production, with augmented antitumor cytotoxic activity. Ipilimumab is an IgG1 monoclonal antibody directed against CTLA-4. In 2011, the FDA approved Ipilimumab for therapy of unresectable or metastatic melanoma based on OS benefit seen with Ipilimumab +/- gp100 vaccine compared to gp100 vaccine alone (HR 0.66–0.68, $P=0.0004$).¹¹⁸ This benefit upon overall survival in second-line therapy was confirmed in a further first-line phase III trial comparing Ipilimumab + DTIC to DTIC alone (11.2 vs. 9.1 months; HR=0.72; $P<0.001$). Trials evaluating Ipilimumab in combination with other therapies including radiation, fotemustine, IFN α 2b, bevacizumab and targeted agents are under way. However trials looking at the inhibitory receptor PD-1 expressed by activated T cells, memory T cells and regulatory T cells has moved forward at even more rapid pace. Binding of PD-1 to its ligands PDL-1/PDL-2 results in down regulation of T cell activity. PDL-1 is expressed by melanoma tumor cells and stroma, and can be used as a biomarker for anti PD-1/PDL-1 directed therapies. Nivolumab (BMS936558) is an anti PD-1 antibody that was evaluated in a phase 1/2 study in patients with advanced cancers including 94 patients with melanoma.¹¹⁹ An ORR of 28% was observed with toxicities that were significantly less than observed with anti-CTLA4 blocking antibodies. BMS936559, an anti PDL-1 antibody showed 20% ORR (9 out of 52 evaluable melanoma patients) in phase 1 trial.¹²⁰ The anti-PDL-1 antibody has shown similar antitumor activity and modest toxicity.¹²¹ Trials are underway evaluating the Merck anti-PD-1 monoclonal antibody MK-3475 and this agent has shown single agent activity as high as 53% response that is being pursued in phase III evaluation against melanoma and lung cancer, along with phase II combinations with IFN and vaccines.

Targeted therapy

The mitogen activated protein kinase (MAPK) and the Akt pathway (PI3K-Akt) are major pathways constitutively activated in a significant proportion of melanomas. The last few years have been an exciting period for targeted therapies in the field of melanoma. Discovery of activating mutations in BRAF V600E/K in 40–50% of cutaneous melanomas, and NRAS mutations in another 20% of cutaneous melanomas, coupled with highly active and specific agents that are capable of inhibiting these pathways has translated into a therapeutic revolution with significant palliative effect for many patients with metastatic melanoma, and improved survival for patients with metastatic melanoma. FDA approved BRAF inhibitors (BRAFi)- Vemurafenib and Dabrafenib (Braf V600E or E and K mutation positive), and the MEK inhibitor (MEKi) Trametinib. Vemurafenib was compared to DTIC in a phase III study with superiority in terms of PFS (5.3 vs 1.6 months, HR 0.26 $P<0.001$) and OS (HR 0.37; $P<0.001$ at 6 months).¹²² Similarly, Dabrafenib showed superiority when compared to dacarbazine in a phase III open label trial that allowed cross over. Median PFS was 5.1 months vs. 2.7 months in the dacarbazine arm (HR 0.30).¹²³ These agents have also shown promise in patients with melanoma brain metastases, a disease site that was notoriously hard to treat and previously often excluded from new trials. Trametinib was compared to dacarbazine or taxol in BRAF V600E/K mutant patients. It was found to be superior to chemotherapy in terms of PFS and OS despite evaluation in a crossover design.¹²⁴ MEKi play a role in patients with BRAF mutant as well as those with the non-overlapping NRAS mutations found in cutaneous and also in uveal melanomas. In combination with BRAFi the findings suggest improved antitumor effects as well as

diminished toxicities, and combinations of BRAFi (Dabrafenib) and MEKi (Trametinib) have received regulatory approval in January 2014, upon the basis of Phase II trial results that make it likely this combination will supersede single agent BRAFi therapy. MEKi continue to be investigated in patients with NRAS mutant disease, and especially uveal (GNAQ/GNA11 mutant) melanoma. Eventual development of resistance to these agents with NRAS or MEK mutations, BRAF truncations and amplification, and increased expression of receptor tyrosine kinases is a problem. Melanoma exhibits a high degree of tumor heterogeneity and a mutational frequency that surpasses all other solid tumors.²⁹ Current clinical trials are evaluating combination therapy with BRAFi and MEKi with the goal to overcome resistance and deliver sustained durable responses, although this may require ternary or more complex combinations given the mutational landscape of the disease. Sorafenib, a multikinase inhibitor, showed response rates of less than 10%¹²⁵ and no benefit in combination with carboplatin and paclitaxel in phase III studies as first line and as second line therapy.¹²⁶ Imatinib has been explored as an agent in cKit positive melanomas. Although it showed limited efficacy in phase II trials, it was shown to have impressive response in patients with activating cKit mutation.¹²⁷ It continues to be evaluated in cKit mutated patients under the auspices of clinical trials. Temsirolimus showed minimal activity in phase II study.¹²⁸

Approaches to inhibit the angiogenesis observed in melanoma, and the elevated VEGF levels that may contribute to immunotherapy resistance have been a longstanding quest. Phase II trials of bevacizumab with IFN α 2b showed stable disease, and studies of other putatively anti-angiogenic approaches including thalidomide and semaxanib did not show promise. VEGF- trap combined with HDIL-2 is currently under evaluation in large phase II (NCT01258855) multicenter clinical trial. Heat shock protein 90, a chaperone for BRAF is up-regulated in melanoma. HSP 90 targeted therapy is a potential adjunct to BRAF inhibitor therapy to overcome BRAFi resistance.

Future directions

The body of knowledge accumulated over the past decades has served as a strong foundation on which the melanoma community is building on at a feverish pace. Every aspect of this field from prevention to surgery to medical therapies has benefitted from this revolution, which in turn has translated into better patient outcomes. As the understanding of the pathophysiology of melanoma grows, so does the armamentarium of therapeutics. Every decade has held out hope for a cure - IFN α 2b in the 1980s, IL-2 in the 1990s, and Ipilimumab and BRAFi in 2000s. The advent of anti PD-1 therapies and an understanding of tumor evasion, with a series of additional checkpoints such as TIM1 and BTLA assure us of exponential improvements in the coming decade. Biomarkers with predictive as well as prognostic utility, and combinations of molecularly targeted anti-tumor therapies and significantly more effective immunotherapy remain the hot topics moving forward. Biomarkers and mutational analysis will form the basis of tailored therapies for patients in terms of both medical therapies and active surveillance. Both lack of and low rates of durable response rate with single agent therapies leads us to believe that effective therapy will be a combination of immunologic, targeted agents and possibly chemotherapy. Understanding the manner in which the tumor is able to overcome or subvert the immune

response to the tumor at the primary site, and in the regional lymphatics is a key challenge. Melanoma has shown its ability to evolve in order to survive as evidenced by rapid rate of genetic change in this tumor. The only system that can match its ability to adapt and counter the tumor is the human immune system. Ultimately the cure for advanced melanoma is likely to reside in awaking and modulating this sleeping giant.

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- The last 30 years has seen a revolution in the field of melanoma.
- Fundamental elements of the surgical, adjuvant medical, and systemic therapy of the disease have been significantly altered toward improved management and better outcomes.
- The intent of treatment for advanced melanoma which was once considered incurable, has changed from palliative to potentially curative.