Adv Ther (2014) 31:945–960
DOI 10.1007/s12325-014-0148-2

REVIEW

Melanoma: Diagnosis, Staging, and Treatment. Consensus group recommendations

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Received: July 19, 2013 / Published online: August 22, 2014

ABSTRACT

The incidence of malignant melanoma is increasing worldwide. In Spain, its incidence is increasing faster than any other cancer type, with a 5-year survival rate of about 85%. The impact and characteristics of malignant melanoma in the Spanish population can be ascertained from the national melanoma registry of the *Academia Española de Dermatología y Venereología*. This review presents consensus group recommendations for the diagnosis, staging and treatment of malignant melanoma in Spain. Incidence and mortality are discussed, as well as evaluation of various prevention and treatment strategies. Prognostic factors, such as BRAF and C-KIT mutations, which are expected to become routine staging procedures over the next few years, are outlined, especially in relation to treatment options. The use of recently approved targeted agents such as ipilimumab, a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitor, and vemurafenib, a BRAF inhibitor, in metastatic disease are also discussed.

Electronic supplementary material The online version of this article (doi:10.1007/s12325-014-0148-2) contains supplementary material, which is available to authorized users.

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Keywords: Diagnosis; Malignant melanoma; Oncology; Prognosis; Spain; Standards; Therapeutics

EPIDEMIOLOGY AND RISK FACTORS

The incidence of melanoma is increasing worldwide [1, 2]. The incidence in Spain is 5.2 cases per 100,000 inhabitants/year [3, 4], with minor changes since the year 1998. The 5-year survival rate in Spain for cases diagnosed between 1995 and 1999 was 85%, with higher rates in women than in men [5].

The Spanish national melanoma registry of the *Academia Española de Dermatología y Venereología* in the period 1998–2011 showed that [2]:

- Melanoma is more common in women (57.2%), though the percentage of males has increased in recent years.
- The mean age at the time of diagnosis is 55 years in women and 57 years in men.
- Histological subtypes include superficially spreading melanoma (60%), nodular melanoma (16%), lentigo maligna melanoma (13%), and acral lentiginous melanoma (5%).
- Predominant locations are the trunk (47%) and head (22%) in males, and the lower extremities (36%) and trunk (26%) in females.
- Mean Breslow tumor thickness is 1.96 mm and 1.53 mm in males and females, respectively. Breslow tumor thickness >4 mm is present in 10.5% of cases.
- Ulceration is observed in 14.3 and 9.9% of tumors in males and females, respectively.

The main known exogenous risk factor for melanoma is exposure to ultraviolet radiation [6]. A personal history of sunburn, a large number of nevi [7, 8], giant congenital nevi [9], a previous melanoma [10], dysplastic nevi, a family history of melanoma [11], certain mutations [12], actinic keratosis, non-melanoma skin cancer [13, 14], and organ transplantation [15] all increase the risk of developing melanoma. Patients with a low socioeconomic status present with thicker lesions [16].

Studies show that continued use of sunscreens reduces the appearance of invasive melanomas [17]. Accessibility to a dermatologist, population information campaigns, and general practitioner training favors early detection [18].

The purpose of this paper is to review the "state of the art" techniques in the diagnosis, staging, pathology, and treatment of melanoma. It was created as a consensus of Spanish clinicians treating this disease and is not meant as a formal guideline, but rather a way for clinicians involved in the management of these patients to remain updated. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

EARLY DIAGNOSIS

Malignant melanoma is detected by the patient in 50% of cases [19], and repeated consultation due to a pigmented lesion should not be neglected [20]. Reported signs include changes in color, size, and shape [19], although irritation or itching is the most common, and often the earliest symptom [21, 22]. In the presence of longitudinal melanonychia (Fig. 1), the possibility of melanoma must be evaluated [10]. Previous pictorial documentation of lesions must be investigated [23].

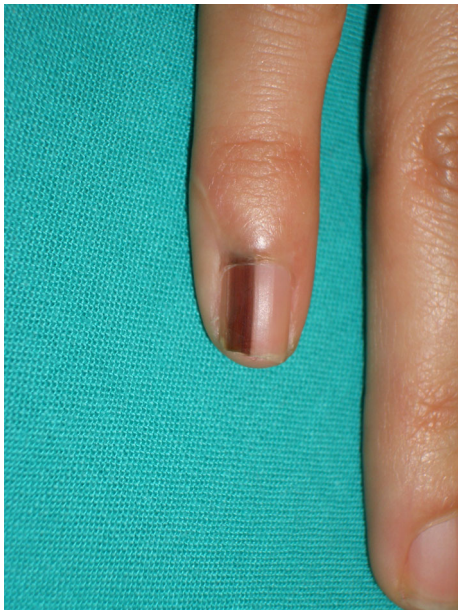

Fig. 1 Striated melanonychia (melanocytic nevus)

Physical Examination

In Spain, around 40% of all melanomas are located on the trunk [24]. The use of diagnostic algorithms is recommended [23], including *A*symmetry, *B*order, *C*olor, *D*iameter, *E*volving (ABCDE) [25–28], Menzies method [25, 29, 30], Argenziano 7-point checklist [26, 28, 30, 31], and pattern analysis [23, 25, 26, 29]. Some melanomas, particularly in their early stages, do not comply with these rules, while other benign lesions occasionally do [32]. Nodular melanoma is usually asymmetrical, with uniform color (Fig. 2) or even amelanotic [33].

Epiluminescence microscopy [34] increases sensitivity, specificity, and diagnostic precision, with a reduction of unnecessary biopsies, but training is required [25, 35]. Physical examination of a patient with suspected melanoma should also include palpation of the corresponding lymphatic drainage territories [36].

Biopsy of Suspicious Lesions

Excisional biopsy with a macroscopic margin of 1–3 mm is the technique of choice [36, 37]. Although the long axis of the excision should follow the direction of tension lines to ensure the best cosmetic effect [23], criteria to completely excise the lesion must prevail. A physician unable to adequately execute this procedure should send the patient to a reference center [10]. For small suspicious lesions (i.e., 8 mm), a large punch biopsy to remove the entire lesion may be indicated. Samples obtained with this procedure can accurately determine Breslow depth and help deciding about surgical definitive treatment.

Location on the face or acral areas may justify the use of alternative biopsy techniques [38]. An incisional biopsy from the most pigmented area should include full skin thickness [10, 38, 39]. Shave biopsy and fine-needle aspiration cytology (FNAC) are not routinely recommended [10, 23, 36], although there could be indications for these procedures in selected cases, in experienced hands.

PATHOLOGY

Histological diagnosis of melanoma is based on cytological and structural characteristics, although some lesions are difficult to differentiate from atypical nevi. In accord with the architectural features of malignant melanocytes, four main histologic patterns have been described: superficial spreading, nodular, lentigo maligna, and acral lentiginous [40]. This classification is now less important, because prognosis and treatment selection can be better defined by other factors.

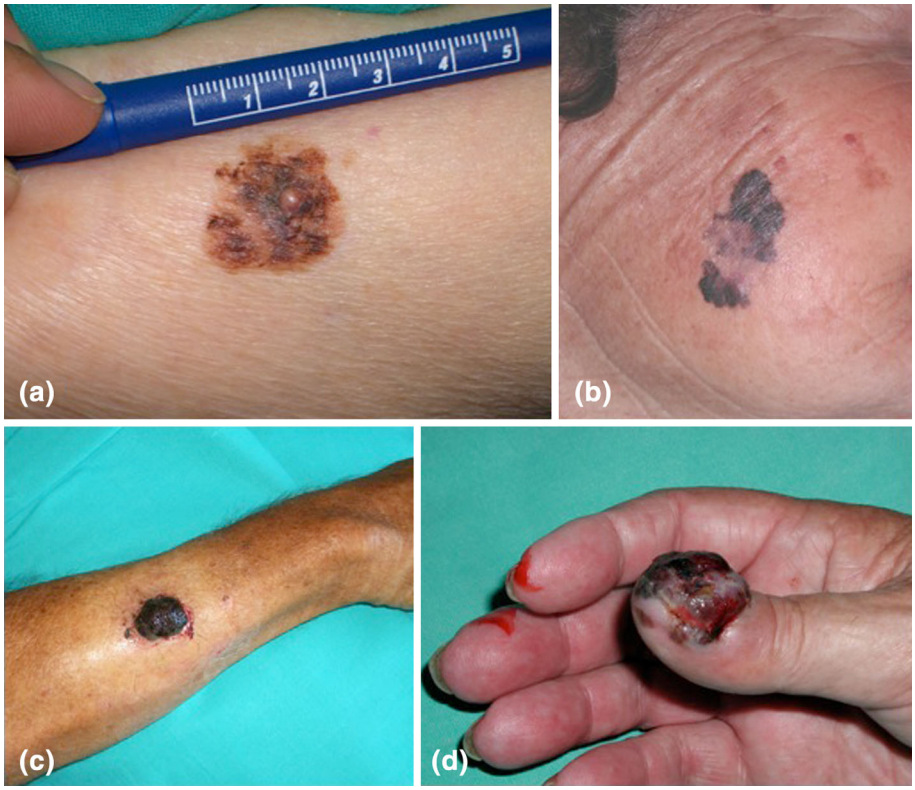

Fig. 2 Examples of cutaneous melanoma. **a** Superficially spreading melanoma. **b** Lentigo maligna melanoma. **c** Nodular melanoma. **d** Acral lentiginous melanoma

Elements to be evaluated in biopsy include asymmetry, epidermal/dermal component, and cytological characteristics. *Asymmetry* refers both to lateral spread of the intraepidermal component and to the distribution of the in-depth dermal proliferation, the cell type and structure, the intensity and distribution of the pigmentation, and host response (inflammation and fibrosis). Primary cutaneous melanoma proliferates with a basal *intraepidermal component*, often spreading in an ascending or pagetoid manner with isolated atypical melanocytes, or forming small groups extending towards the granular layer of the epidermis. In its dermal component, melanoma can adopt many patterns, ranging from diffuse with single cells or nests to micro- or macro-nodular, with marked intratumor heterogeneity and without maturation in depth. Reactive changes including inflammation, fibrosis, desmoplasia, and vascular proliferation are common. "Consumption" or *erosion of the epidermis* consists of thinning of the basal and suprabasal layers, with loss of the epidermal crests in areas in direct contact with the neoplastic melanocytes. It is observed in 86% of melanomas and in only 9.6% of all Spitz nevi [41]. In cytology, melanoma cells are highly variable: polygonal, rounded, oval, fusiform, dendritic, signet ring, etc. Cell size ranges from that of a lymphocyte to a "giant" cell, and atypical multinucleated cells are common. An important feature is the abrupt transition between the different types of cell groups.

The pathologist provides information about key prognostic factors in early-stage disease: tumor thickness, ulceration, mitotic index, and

the presence of satellite lesions. Other useful information is described below.

Breslow Tumor Thickness

Breslow tumor thickness is the most important prognostic factor in clinically localized melanoma [42], representing an independent prognostic and survival variable [43]. Breslow tumor thickness is the maximum vertical dimension of tumor infiltration from the top of the granular layer of the epidermis (or base of ulcer) to the deepest lying tumor cell. The American Joint Committee on Cancer (AJCC) establishes four prognostic categories: up to 1 mm, 1–2 mm, >2 mm, and >4 mm. For thin melanomas (<1 mm), the 5-year survival rate is >90%, while the rate for lesions >4 mm with ulceration is about 45% [43].

Clark Level

The level of tumor invasion is closely related to tumor thickness [44], but its importance has decreased over time.

Growth Phases

Growth phases include radial growth, with very low metastatic potential, and vertical growth, where the tumor acquires increased metastatic potential [45, 46]. In radial growth phase, the tumor is intraepidermal or microinvasive to the papillary dermis, forming nests containing <15 cells and without mitotic figures in the infiltrating component with no regression features [45, 46].

Ulceration

Ulceration is defined as the absence of epidermis above the tumor. Its incidence increases with tumor thickness, and is associated with poorer survival in all tumor thickness categories [43]. Ulceration produced by melanoma must be distinguished from ulceration caused by treatment or friction [43].

Mitotic Index

Mitotic index reflects tumor proliferation and is therefore inversely correlated with prognosis and survival [43, 47]. The presence of mitosis increases the stage from T1a to T1b in lesions less than 1 mm depth. This may be important, as the latest AJCC staging classification recommends sentinel lymph node biopsy (SLNB) in patients with T1b lesions [48].

Satellitosis

Satellitosis is defined as a group of neoplastic cells ≥0.05 mm in diameter, located in the dermis or subcutaneous cellular tissue <5 cm from the primary tumor [43]. The presence of satellite cells worsens prognosis [49].

Immunohistochemistry

Immunohistochemistry (IHC) can assist in distinguishing melanocytic from non-melanocytic lesions when the tissue of origin is uncertain. S100 is very sensitive, but not very specific, and additional antibodies are required to confirm the nature of S100-positive neoplasms. Other common markers include melanoma antigen recognized by T-cells 1 (MART-1; also called Melan-A), microphthalmia-associated transcription factor (MITF), human melanoma black 45 (HMB-45), and Sox-10 [50]. Additional gene markers have been described to provide prognostic information in difficult cases.

Molecular Genetic Factors

A group of patients have been identified with loss of $p16^{INK4}$, presence of B cell lymphoma 6 (BCL-6), a high proliferation index (Ki67 >20%), or p21 positivity, with a poorer prognosis and shorter survival (<6 years) [51]. Also, genes implicated in epithelial–stromal transition are over-expressed in primary melanomas in the vertical growth phase with metastatic potential. A systematic review, "Reporting recommendations for tumor marker prognostic studies" (REMARK), identified $p16^{INK4}$, surviving, and p53 as the most useful markers to determine outcome [52]. New high-throughput modalities can help identify multi-gene or multi-protein profiles related to prognosis or to treatment response.

STAGING

Early Stage

Several staging guidelines for the evaluation of patients with localized and metastatic melanoma are available [53–55], but their impact in clinical practice varies considerably. Physical examination, with special attention to other suspiciously pigmented, satellite or in-transit lesions, and regional lymph nodes, is emphasized as a basic and mandatory staging procedure. In low-risk melanomas (≤1 mm) no other investigations are considered necessary, whereas blood testing and radiological imaging are recommended in locally advanced disease.

SNLB is recommended in melanomas ≥1 mm thick and no clinical ultrasound evidence of local recurrence or in-transit metastasis, and in melanomas <1 mm with ulceration, regression signs or ≥1 mitoses per mm^2 [53, 55]. Histology of the sentinel node, involving multiple sections, comprises standard hematoxylin–eosin staining and, when this proves negative, IHC for HMB-45 and Melan-A.

Some groups advocate preoperative ultrasound in combination with ultrasound-guided FNAC to detect regional lymph node metastases. In the event of a negative cytological result, SLNB must be performed, but if FNAC is positive the patient should undergo complete lymphadenectomy [56].

Locally Advanced and Metastatic Melanoma

Potentially resectable lymph node metastases require accurate staging to prevent unnecessary surgery. Computed tomography (CT) is the most widely used imaging method for tumor staging, surveillance, and the assessment of therapeutic response, but there are also roles for ultrasound, magnetic resonance imaging (MRI) and 2-[18F]-fluoro-2-deoxy-D-glucose positron-emission tomography combined with CT (FDG PET–CT).

The conventional approach to advanced melanoma staging includes the combination of brain MRI together with either contrast-enhanced CT of the chest, abdomen, and pelvis, or PET–CT [57]. Whole-body MRI is an appropriate alternative to CT without ionizing radiation, particularly in young patients with advanced melanoma [58]. FDG PET–CT is superior in detecting bone and subcutaneous metastases, and is comparable with CT for detection of liver, abdominal, and lung metastases [59]. Since MRI with intravenous contrast media is more sensitive than CT or PET–CT for the detection of brain metastases [57], a combination of brain MRI and FDG PET–CT could be considered the most accurate technique for stage IV disease.

SURGICAL TREATMENT OF PRIMARY MELANOMA

Surgical treatment comprises resection of the primary tumor (after histological study and selective SLNB), regional disease, and disseminated disease. Removal of the primary lesion is typically done at the time of clinical diagnosis through an excisional biopsy with a margin of 1–3 mm, and should not be done with wider resections to avoid compromising the SLNB. After diagnosis, complete removal with safe margins of the primary lesion or margin widening to avoid local recurrence should be performed simultaneously with the SLNB. Accepted surgical margins in relation to Breslow tumor thickness are shown in Table 1 [60]. Tumor resection with margins >2–3 cm does not improve local course of the disease. In depth, en bloc resection must include the skin and subcutaneous cellular tissue down to the aponeurosis of the underlying muscle layer. Reconstruction depends on the location and magnitude of resection; primary suturing or neighboring skin flaps (advancement-transfer and rotation) can be used, and free skin grafting may prove necessary.

SLNB should be done in all patients without clinical or radiological evidence of lymph node metastases by injecting 99Tc around the primary lesion (if not removed previously) or the scar, and confirmed by lymphoscintigraphy preoperatively. If no SNLB is performed before surgery, no further surgery should be done. Lymph node positivity, preoperatively or by SLNB, requires lymphadenectomy of the region where the node is located, without thorough evidence when micrometastases are concerned.

Table 1 Surgical margins in relation to lesion thickness

Breslow tumor thickness (mm)	Resection margin (cm)
0.0 (in situ)	0.5
<1.0	1.0
1.0–4.0	2.0
>4.0	2.0–3.0

ADJUVANT THERAPY

High-risk melanoma patients, defined as stages IIB–III (i.e., ulcerated tumors with Breslow tumor thickness 2–4 mm, tumors >4 mm thick, and the presence of positive lymph nodes), have been the subject of adjuvant studies, with interferon as the only drug offering well-defined benefit to date. Guidelines agree that the options for high-risk patients are adjuvant interferon and participation in clinical trials [53, 55].

High-dose interferon comprises a 4-week daily intravenous induction phase, followed by a 48-week subcutaneous maintenance phase three times weekly. Medium- and low-dose interferon-alpha (5–10 and 3 MU, respectively) is administered thrice weekly over 18–60 months. In addition, pegylated interferon can be administered once weekly, although optimal duration of therapy has not been established.

Table 2 summarizes the main clinical trials involving adjuvant interferon therapy [61–74]. Trials of high- and intermediate-dose interferon, and one trial with pegylated interferon, show positive progression-free survival benefits [63–65, 68, 70–72], but no studies of interferon monotherapy have demonstrated improved overall survival versus observation. Three meta-analyses concluded that interferon increases progression-free and overall survival rates by 7 and 3%, respectively, independently of dose and duration of treatment [75–77]. Furthermore, two European

Table 2 Main randomized clinical trials involving adjuvant interferon therapy in patients with melanoma

Trial	Patients	Disease stage	Treatment duration (months)	Comparator	PFS effects	OS effects
High doses						
NCCTG [63]	264	T2–4N0 T1–4N+	4	Observation	−	−
E1684 [72]	287	T4N0 T1–4N+	12	Observation	+	+
E1690 [70]	642	T4N0 T1–4N+	12	Low-dose interferon; observation	+	−
E1694 [71]	880	T4N0 T1–4 N+	12	Vaccine	+	+
E1697[a] [61]	1,150	T2–4N0 T1–4N1	1	Observation	−	−
Medium doses						
EORTC18952 [64]	1,388	T4N0 T1–4 N+	12 vs. 24	Observation	−12 vs. +24 months	−
EORTC18991[b] [65]	1,256	T1–4N+	60	Observation	+	−
DeCOG[a] [69]	650	T2–4N0	24	Low-dose interferon	–	−
Scandinavia[a] [68]	855	T4N0 T1–4N+	12 vs. 24	Observation	+12 vs. −24 months	−
Low doses						
Austria [73]	311	T2–4N0	12	Observation	+	−
France [66]	499	T2–4N0	18	Observation	+	−
United Kingdom [67]	674	T4N0 T1–4N+	24	Observation	−	−
DeCOG [74]	444	T1–4N+	24	Interferon + dacarbazine; observation	+	+
WHO [62]	444	T1–4N+	36	Observation	−	−

EORTC European Organisation for Research and Treatment of Cancer, *NCCTG* North Central Cancer Treatment Group, *OS* Overall survival, *PFS* Progression-free survival, *WHO* World Health Organization, *DeCOG* Dermatologic Cooperative Oncology Group

+, denotes a statistically significant difference for interferon; −, denotes no difference

[a] Trial not included in the meta-analyses

[b] Pegylated interferon

Organization for Research and Treatment of Cancer trials suggest that patients with a low lymph node tumor burden (positive SLNB) benefit most from adjuvant therapy [64, 65], and a study of pegylated interferon suggested that ulceration may be another predictor of treatment benefit [65].

Adjuvant Radiotherapy

Adjuvant radiotherapy may help to prevent locoregional disease recurrence. The recurrence rate after radiotherapy was 11%, compared with 50% in patients who underwent surgery alone [78]. It is recommend when the primary lesion has infiltrated or is very close (<1 mm) to surgical margins, in the presence of tumor satellitosis, perineural infiltration, and for early or multiple recurrences. Regional radiotherapy after elective lymph node resection reduces lymph node disease recurrence rate by 20–50%.

METASTATIC MELANOMA

Prognostic Factors

Survival and response to chemotherapy in stage IV depend upon the location of the metastases, with lymph node or subcutaneous metastases having a better prognosis than lung metastases, which in turn have a better prognosis than lesions in other visceral sites [79, 80]. Lactate dehydrogenase levels are also important to define prognosis.

Surgical Treatment

Metastasis resection may be the treatment of choice in a selected group of patients [81–84]. Cases most amenable to surgery are those involving single metastases, and especially when relapse has occurred after a long follow-up period [83]. Radiofrequency ablation may be considered in some cases [85].

Radiotherapy

Radiotherapy, considered the best pain-relief treatment in bone metastases, can play a very important role in palliating multiple symptoms of metastases. Treatment preferentially involves short cycles, with palliative efficacy shown in up to two-thirds of cases [86–88]. Treatment generally consists of 20 Gy in 1 week or 30 Gy over 2 weeks. Metastases in long bones or in weight-bearing bones involve a risk of fracture; therefore, it is advisable to anticipate pathological fracture, even in the absence of pain, to prevent fracture and loss of patient quality of life. Surgical fixation is indicated in lesions that destroy >80% of the cortical layer, and in the case of lytic lesions > 2.5 cm in size. Following surgical stabilization, irradiation is recommended for the treatment of microscopic disease.

Holocranial radiotherapy (30 Gy in 10 sessions) is an effective palliative treatment of brain metastases. Improvement is observed in 60–70% of cases [89]. The duration of treatment response is brief, however, and neurological tumor progression is the usual cause of death. Stereotactic radiosurgery may be an alternative to surgery in some cases (up to 3 lesions <3 cm in size) [90, 91]. Disease control rates reach 90% with this technique, with survival durations of 7–12 months [88].

Treatment of In-Transit Metastases

In-transit metastases should be resected whenever possible, and local treatment

options, such as intralesional therapy [92], cryotherapy [93], laser therapy [94], radiotherapy [95], and electrochemotherapy [96, 97] can also be used. Amputation of extremities is not indicated since it does not improve survival; therefore, when in-transit metastases are not amenable to resection and the disease is located in the extremities, isolated limb perfusion is the treatment of choice [98]. Perfusion can be performed with melphalan with or without tumor necrosis factor [99, 100].

Systemic Treatment

New agents have revolutionized the landscape of advanced melanoma. Some of these agents enhance the activity of the immune systems through the blockade of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD1) receptors. These receptors act as natural brakes for T-cells once the immune response has been initiated. As a consequence of blocking CTLA-4 and PD1, T-cells can recognize and destroy tumor cells more efficiently. Two phase III trials of the anti-CTLA-4 antibody ipilimumab have demonstrated superiority over dacarbazine (first line) and a vaccine (second line), with 20% of patients remaining alive in the long-term [101, 102]. Anti-PD1 antibodies, such as nivolumab and pembrolizumab, also enhance the activity of the immune system and induce durable responses in nearly 50% of patients [103, 104]. Preliminary results from the combination of ipilimumab and nivolumab show fast responses in two-thirds of patients, although these impressive results require confirmation [105]. Factors predicting response to anti-CTLA-4 or anti-PD1 antibodies have not been identified thus far, indicating that these drugs could be used in the general population of patients with advanced melanoma.

Approximately, 50% of cutaneous melanomas harbor activating mutations in BRAF, a key change that drives proliferation. Vemurafenib and dabrafenib are selective BRAF inhibitors that target the V600 mutant forms of this protein. Phase III studies of these agents demonstrated superiority in response rate, progression-free survival and overall survival over classical chemotherapy [106–108]. MEK inhibitors, such as trametinib, can also induce responses in BRAF-mutated melanoma [109]. The majority of patients treated with selective inhibitors experience tumor shrinkage, but resistance usually appears after several months of therapy. A phase II study suggests that the combination of a MEK inhibitor and a BRAF inhibitor increases response rate and prolongs disease-free survival, compared with single-agent therapy [110]. MEK inhibitors are also in development for NRAS-mutated melanoma [111]. As specific tyrosine-kinase inhibitors, BRAF and MEK inhibitors require the presence of a mutation in their targets to have clinical activity. Investigation is now focused on the mechanisms of resistance that appear in most patients, accounting for tumor re-growth after a few months of therapy. A better understanding of the molecular biology of melanoma can also lead to the identification of new therapeutic targets.

Conventional chemotherapy can be used whenever new drugs or clinical trials are not available. Options include dacarbazine (with a response rate of 15–20% and a progression-free survival of 6 months), fotemustine, or temozolomide [112–114]. Overall survival with any of these agents is 7–9 months.

DISCUSSION AND CONCLUSION

Incisional biopsy of any suspicious lesion and review by an experienced pathologist is a key

element in disease diagnosis. New IHC and molecular markers may provide additional information in selected cases, although controversy remains about the optimal combination of these markers.

Early diagnosis contributes to high rates of curation in developed countries, but stage IV disease remains incurable in the vast majority of patients. However, the discovery of BRAF V600 mutations in 40–50% of melanomas, together with a better understanding of the function of CTLA-4 and PD1 suppressor mechanisms, has led to the development of new targeted treatments. These advances clearly impact tumor response and survival, and have changed the therapeutic approach to metastatic melanoma. A new horizon of combination therapies is expected in the near future, and participation in clinical trials should be strongly encouraged.

ACKNOWLEDGMENTS

Funding for the article processing charges was provided by Merck Sharp & Dohme, Spain. Technical editing and manuscript styling was provided by Andrea Bothwell and Kenneth McCrea on behalf of Springer Healthcare Communications, with funding provided by Merck Sharp & Dohme, Spain. All authors are members of the *Grupo Español Multidisciplinar de Melanoma* (GEM). All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. AB, LC, EE, RFM, SMA, JCMC, LRB, and JLRP declare no personal, financial, commercial, or academic conflict of interest.

Compliance with ethics guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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