CONSENSUS STATEMENT

Initial Evaluation, Diagnosis, Staging, Treatment, and Follow-up of Patients with Primary Cutaneous Malignant Melanoma. Consensus Statement of the Network of Catalan and Balearic Melanoma Centers

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Identification and Follow-up of Suspicious Lesions or Individuals at High Risk for Developing Melanoma

While the usefulness of screening the general population for melanoma has not been established, regular dermoscopic monitoring by a dermatologist of individuals at high risk for developing malignant melanoma (MM) is generally recommended; this group includes patients with multiple clinically atypical moles and those with a personal or family history of MM.\(^1\)\(^-\)\(^3\) Physicians should draw up a surveillance plan for patients in this high-risk group to ensure early identification of malignant lesions or lesions with a risk of developing into malignant melanoma (lesions that meet the ABCDE criteria of asymmetry, border irregularity, color variegation, diameter >6mm, or rapid evolution). Taking into account the presence of one or more of the following known risk factors for developing MM, the plan should define the type and frequency of follow-up in each case (6-monthly or annual visits), specify whether manual or digital dermoscopy (body mapping) should be used,\(^4\) and include a family risk study\(^5\)-\(^10\):
1. Phenotype: light eye color, fair skin phototype (I or II), blonde or red hair, the presence of multiple freckles or solar lentigines, numerous typical nevi (>50), numerous clinically atypical nevi (as per the ABCDE criteria), dysplastic nevi syndrome (>100 nevi including 1 or more with a diameter >6mm and 1 or more with a dysplastic histology).

2. History of MM and/or multiple neoplasms in a first-degree relative.

3. Personal history of MM

A personal history of MM increases the individual’s risk of developing a second primary melanoma by a factor of 10, with maximum risk occurring during the 2-year period following diagnosis of the first primary lesion. Patients with a family history of MM who have multiple atypical nevi are at increased risk for developing melanoma. In our region (Catalonia and the Balearic Islands), some of the families with familial melanoma have been found to have mutations in the CDKN2A and CDK4 genes, which are associated with a lifetime risk of developing melanoma ranging from 60% to 90% (Table 1). In these probands with a high level of suspicion and in patients with multiple primary melanomas, genetic diagnosis should be carried out in the context of a genetic counseling program. The Hospital Clinic in Barcelona has a genetic counseling program that deals specifically with familial melanoma and similar services exist throughout Spain. Other centers offering such counseling include the Instituto Valenciano de Oncología (Valencia), the Hospital Virgen de la Arrixaca (Murcia), and other centers in the Basque Country, Madrid, and Galicia.

### Diagnosis and Clinical Staging of Primary Melanomas

**Preoperative Assessment of the Primary Tumor**

When dealing with a melanocytic lesion and clinical suspicion of MM, the medical history obtained from the patient should include the following details:

1. Evolution of the lesion, including the following information in addition to any other relevant details: the chronology of the lesion; the signs or symptoms that gave rise to the consultation; the presence or absence of bleeding, itching, or pain; any changes in the color, shape, or size of the lesion; the existence of a precursor lesion and any prior manipulation or treatment of the lesion.

2. The results of the macroscopic study of the tumor including details of the site, findings on palpation, the presence of papules or nodules, size, pigmentation, clinical type, ulceration, areas of regression, adjacent nevi, etc.

3. Description of the results of epiluminescence microscopy (dermoscopy).

4. Graphic documentation of the evidence that gave rise to clinical suspicion of MM.

**Clinical Diagnosis and Skin Biopsy**

All lesions suspected of being MM should be biopsied, and specimens should be sent to the pathology department for histologic confirmation of the diagnosis. Whenever possible the biopsy should be excisional and include the entire lesion, with margins between 2 mm and 5 mm to avoid modifying the lymphatic drainage of the affected area. Avoid manipulation of the suspicious lesion with needle pricks, curetage, shave excision, and treatment with electrocoagulation, laser, cryotherapy, or any other technique that might complicate correct histological study of the excised sample. Occasionally (when clinical suspicion is low or when the lesion is located on the face or any area where excision would result in disfigurement) an incisional biopsy may be carried out (punch biopsy). In such cases, the thickest portion of the lesion should be biopsied (as assessed by palpation or using dermoscopic criteria).

**Pathologic Diagnosis**

The pathology report on an malignant melanocytic lesion should conform to the consensus guidelines published recently by various Spanish working groups. According to these recommendations, all pathology reports must include the characteristics listed in Table 2, and negative results must be explicitly noted. When a value cannot be identified in the histologic specimen, this fact must also be explicitly noted in the report. When a patient who has been diagnosed with MM in another hospital is referred for follow-up and/or sentinel node biopsy (SNB), the referral hospital should request a slide and/or the paraffin block for reassessment.

### Table 1 Incidence of CDKN2A Mutations Detected in the Blood of Patients with Melanoma

<table>
<thead>
<tr>
<th>CDKN2A Mutations</th>
<th>Risk</th>
<th>%</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic melanoma</td>
<td>Total</td>
<td>2.3</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>1.2</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>3.8</td>
<td>1.66</td>
</tr>
<tr>
<td></td>
<td>Not multiple</td>
<td>1</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Multiple (2 melanomas)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple (3 or more)</td>
<td>27.8</td>
<td>16.34</td>
</tr>
<tr>
<td></td>
<td>Age &gt;40 y</td>
<td>1.1</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Age &lt;40 y</td>
<td>5</td>
<td>2.21</td>
</tr>
<tr>
<td>Familial melanoma</td>
<td>Two family members with melanoma</td>
<td>0.19</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Three family members with melanoma</td>
<td>0.25</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Three or more family members with melanoma</td>
<td>0.43</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Four family members with melanoma</td>
<td>&gt;0.75</td>
<td>–</td>
</tr>
</tbody>
</table>

*Data obtained from the study of over 700 cases of sporadic melanoma, over 150 cases of multiple melanomas, and more than 50 families with familial melanoma studied in our area.*
Table 2  Histopathologic Characteristics that Must be Included in the Pathology Report of Melanoma

<table>
<thead>
<tr>
<th>Macroscopic description of the anatomical site and the biopsy sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of excision (incisional or excisional biopsy, shave excision, curretage, etc)</td>
</tr>
<tr>
<td>Clinicopathologic type</td>
</tr>
<tr>
<td>Tumor thickness (Breslow depth)</td>
</tr>
<tr>
<td>Level of invasion (Clark)</td>
</tr>
<tr>
<td>Mitotic rate (number of mitoses per mm²)</td>
</tr>
<tr>
<td>Vertical growth phase (yes/no)</td>
</tr>
<tr>
<td>Ulceration (yes/no)</td>
</tr>
<tr>
<td>Regression (yes/no)</td>
</tr>
<tr>
<td>Lymphocytic invasion (yes/no)</td>
</tr>
<tr>
<td>Vascular involvement (yes/no)</td>
</tr>
<tr>
<td>Perineural involvement (yes/no)</td>
</tr>
<tr>
<td>Histologically confirmed satellite metastasis</td>
</tr>
<tr>
<td>Width of disease-free excision margins in mm (lateral and deep)</td>
</tr>
<tr>
<td>Precursor lesion (melanocytic nevus) (yes/no)</td>
</tr>
</tbody>
</table>

Optional Information

- Plasmacytic infiltration
- Semiquantitative assessment of regression and inflammatory infiltration
- Melanoma cell types and variants (nevoid, balloon cell, small cell, folliculotropie, spitzoid, etc.)

Taken from our protocol for pathology reports in primary melanoma

Initial Assessment of the Melanoma Patient

Medical History

The preliminary clinical assessment of all patients diagnosed with melanoma should include a detailed medical history with particular attention paid to all aspects pertinent to MM. In addition to other clinical characteristics, the following should be noted:

1. Personal and family history of MM or dysplastic nevus syndrome
2. Personal and familiar history of cancer
3. Skin phototype
4. Habits of exposure to sun (pattern of solar exposure: intermittent, chronic, etc), amount of time spent outdoors in work and leisure activities, number of severe sunburns, use of UV-A tanning lamps, etc)
5. The symptoms that gave rise to the consultation (itching, pain, bleeding, changes in the color or size of the lesion, etc)
6. Site and diameter of the lesion
7. Presence of areas suggestive of regression
8. Presence of clinically atypical nevi
9. Presence of a precursor lesion

A general clinical history should also be recorded and should include information on any symptoms that might suggest the presence of metastasis (toxic syndrome, localized pain, cough, neurological symptoms, bleeding in the digestive tract, etc) and any concomitant diseases, particularly conditions that might limit future medical or surgical treatment.

Physical Examination

The dermatological examination should be complete and include the scalp, genital region, and oral mucosa. Particular attention should be paid to the detection of possible precursor lesions (clinically atypical nevi), additional suspicious pigmented lesions, and possible cutaneous metastases of the primary melanoma. Patients should also undergo a general physical examination with particular attention to the examination of the regional lymph nodes and the presence of subcutaneous masses or nodules.

Additional Investigations in the Study of Initial Spread

The clinical and pathologic classification currently recommended for staging patients with MM is the American Joint Committee on Cancer (AJCC) prognostic staging system (seventh classification) published in 2009 (Table 3). Prior pathologic examination of the primary tumor and of an SNB (if indicated) are necessary for the application of this system.

Lymph Node Staging. Indications for Sentinel Node Biopsy

Sentinel node technology has made possible selective assessment of the regional lymph nodes at greatest risk for metastasis due to lymphatic spread, thereby limiting the need for radical surgical intervention (lymphadenectomies) and/or adjuvant treatments in patients in whom metastasis is detected. Consequently, the chief utility of SNB in patients with MM, almost universally accepted by the scientific community, is its role as a precise staging tool, and its use is essential in the case of patients participating in clinical trials. However, some authors consider the routine use of SNB to be controversial because it has not yet been shown to have any beneficial impact on overall survival.

Criteria for Sentinel Node Biopsy

Table 4 summarizes the currently accepted criteria for the selection of candidates for SNB in MM.

In the preliminary assessment of tumor spread in patients without clinically evident nodal involvement, ultrasound of the regional nodal basin should not replace SNB in routine clinical practice. Ultrasound can, however, be useful before SNB when clinical palpation is problematic (in obese patients and patients with prior surgery in the area to be explored, such as those who have undergone inguinal herniorrhaphy) and in hospitals that do not perform SNB or refer patients to other centers for SNB. SNB is not recommended in patients at low risk for MM (stages 0 and IA) and when there is no clinical suspicion of nodal involvement. In the protocols of some hospitals, SNB may be indicated in invasive low-risk primary tumors (Breslow...
depth <1 mm, nonulcerated) if there is clear evidence of histologic regression or other features indicating a poor prognosis.35-40 The best time to obtain a SNB is during the definitive surgical excision procedure undertaken to increase the safety margins around a primary tumor (or during the definitive wide excision of a tumor when the initial biopsy was incisional). Pathologic examination of sentinel lymph nodes should be exhaustive, and requires an approach that

Table 3  Current Clinicopathologic Classification for Melanoma Published by the American Joint Committee on Cancer (AJCC)°

<table>
<thead>
<tr>
<th>T Classification</th>
<th>Thickness, mm (Breslow Depth)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of any primary tumor</td>
<td>Either</td>
</tr>
<tr>
<td>Tis</td>
<td>In situ</td>
<td>Either</td>
</tr>
<tr>
<td>T1</td>
<td>≤ 1</td>
<td>a: without ulceration and with mitosis &lt;1/mm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration or mitoses &gt; 1/mm²</td>
</tr>
<tr>
<td>T2</td>
<td>1.01-2.0</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01-4.0</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>&gt; 4.0</td>
<td>a: without ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: with ulceration</td>
</tr>
<tr>
<td>N Classification</td>
<td>No. of Metastatic Nodes</td>
<td>Nodal Metastatic Burden</td>
</tr>
<tr>
<td>N1</td>
<td>1 node</td>
<td>a: micrometastasisb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: macrometastasisc</td>
</tr>
<tr>
<td>N2</td>
<td>2-3 nodes</td>
<td>a: micrometastasisb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: macrometastasisc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: in transit or satellite metastases without metastatic nodes</td>
</tr>
<tr>
<td>M Classification</td>
<td>Site</td>
<td>Serum Lactate Dehydrogenase</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous,</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>or nodal metastases</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

°Adapted from Balch et al.20

©Micrometastases are diagnosed by pathologic and/or immunohistochemical examination of the nodes dissected in the course of sentinel node biopsy.

©Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension in the pathologic examination.
1. Standard workup including complete blood count and biochemistry, which should include alkaline phosphatase, gamma-glutamyltransferase, and lactate dehydrogenase (LDH). Measurement of other markers, such as S-100β, melanoma inhibitory activity, and reverse transcription polymerase chain reaction of tyrosinase messenger RNA in circulating blood, should also be considered.

2. Posteroanterior and lateral plain chest radiograph

3. Electrocardiogram (in cases in which SNB is indicated as part of the preoperative preparation and in candidates for adjuvant treatment [interferon])

In patients with low-risk or medium-risk MM (stages IA, IB, and IIA), no additional tests and examinations are routinely carried out, although some hospitals recommend abdominal ultrasound in stages IB and IIA. When there are clinical grounds for suspecting metastasis, the additional tests required in each case to confirm diagnosis and facilitate staging should be ordered (computed tomography [CT], ultrasound, nuclear magnetic resonance imaging [MRI], scintigraphy, etc). In patients with high-risk invasive melanoma (stages IIB, IIC, and III), further investigation is recommended even in patients with a normal physical examination on diagnosis because of the high probability of occult distant metastasis. The following examinations are recommended at the initial visit prior to definitive surgical treatment (SNB or lymphadenectomy): chest, abdominal, and pelvic CT (or chest CT and abdominal ultrasound), cranial MRI or CT (optional), cervical CT (in the case of tumors on the head or neck), and bone scintigraphy (optional). In our region, positron emission tomography (PET) is only ordered for melanoma patients who have distant metastasis, either during initial staging and/or when there is a suspicion of recurrence, and only when a curative therapeutic approach is under consideration depending on the results of the investigation (for example when surgical intervention is being considered for a single metastasis or when the images obtained with other methods are unclear).

However, with the greater availability of this imaging method and its use in combination with other techniques (PET-CT), it is now possible to evaluate on a case-by-case basis the usefulness of the technique in the initial assessment of high-risk melanoma (AJCC stages IIB, IIC, and III) and in patients in whom nodal metastases are detected at initial presentation, especially in the case of melanoma of unknown origin (see below).

### Additional Investigations for Visceral Staging

In addition to the physical examination and the pertinent medical history obtained during the preliminary assessment, the following investigations should also be carried out to complete staging in all patients diagnosed with invasive MM except those with stage 0 melanoma in situ.

1. Posteroanterior and lateral plain chest radiograph
2. Electrocardiogram (in cases in which SNB is indicated as part of the preoperative preparation and in candidates for adjuvant treatment [interferon])

### Treatment of Patients with Localized MM

Invasive MM is a complex tumor that must be managed by a multidisciplinary team of specialists. Whenever possible, the team should be coordinated and organized into specialist committees.

### Treatment of the Primary Tumor

The treatment for primary cutaneous melanomas is wide local excision of the tumor. Radiotherapy and other treatments (imiquimod, cryotherapy, etc) are only used to treat primary tumors when surgery is not feasible (inoperable patients) or when complete extirpation of the lesion would be highly disfiguring (for example a large lentigo maligna on the face). The ideal procedure is en bloc resection with margins no greater than 0.5 cm when the suspicious lesion is being biopsied (an excisional biopsy). This margin will be adequate in the case of the thinnest tumors (melanoma in situ) and will not affect
the lymphatic drainage of the area around the tumor in patients who subsequently undergo procedures such as lymphoscintigraphy and the identification and biopsy of sentinel nodes. The interval between the diagnostic biopsy and the definitive surgical intervention should always be as short as possible. Once the lesion has been excised and the diagnosis of MM confirmed, a re-excision procedure is scheduled to increase the safety margins of the initial excisional biopsy. The lateral margin width should be measured from the scar of the simple excision, discounting the 2 to 5 mm margin extirpated during the initial tumor resection from the total width required. The minimum safety margin is dictated by the thickness of the tumor measured using a micrometer (Breslow depth). The deep excision extends down to the muscle fascia but does not include it.\textsuperscript{6-10,22,23} Several randomized controlled trials have shown that the ideal lateral margin in each case will depend on the depth of the lesion (Breslow depth) and that increasing safety margins beyond 3 cm is not associated with any benefit.\textsuperscript{60-68} Analysis of past experience has led to a reduction in the margins previously recommended (Table 5). Patients in the studies cited above were stratified according to the classification systems in use at the time, which did not take into account the importance of ulceration of the primary tumor in staging disease. Data are now needed from similar studies taking into account the TNM staging of the tumor, but to date no such studies have been published. When SNB is indicated (as per the above criteria), the safety margins should ideally be increased when the sentinel biopsy procedure is carried out or, if this is not possible, following SNB. Surgical treatment of the primary tumor must sometimes be adapted to the anatomical peculiarities associated with the site, certain large tumors, or the patient's medical situation. In the case of subungual tumors, amputation below the distal interphalangeal joint is recommended. However, in the case of stage 0 subungual tumors (melanoma in situ), a conservative surgical approach should be considered (extirpation plus graft or plastic surgery). Likewise, when the melanoma is located on other sites on the fingers or on the palms, soles, or other areas of the hands or feet, a conservative treatment of the limb should be considered as long as complete excision with adequate safety margins can be achieved. Acceptable reconstructive techniques include grafts, flaps, and healing by second intention. In the case of tumors on the fingers, a disarticulation proximal to the tumor can also be performed.\textsuperscript{69} Mohs micrographic surgery has also been shown to be a valid option when a tumor proves difficult to delimit or is located at an anatomical site where it may be difficult or disfiguring to ensure adequate safety margins using other methods.\textsuperscript{70-72}

### Treatment of Nodal Disease

Metastasis to the regional lymph nodes is treated by surgery (lymphadenectomy), which in selected cases may be followed by an adjuvant treatment (radiation therapy, immunotherapy, etc.). The different lymphadenectomy procedures used depending on the anatomic area of the lymphadenopathy are shown in Table 6. Selective lymph node dissection should be performed when there is no clinical evidence of regional disease but the histopathologic study of the sentinel node or nodes reveals the presence of micrometastases. Therapeutic lymphadenectomy is indicated in patients with obvious lymph node involvement (clinical suspicion after palpation or on the basis of ultrasound, CT, or PET findings) that has been confirmed histologically (percutaneous fine needle aspiration biopsy [FNAB] or ultrasonically-guided FNAB depending on the site).\textsuperscript{6-10,22,23} The following relative contraindications should be taken into account when indicating lymphadenectomy:

<table>
<thead>
<tr>
<th>Site</th>
<th>Type of Lymphadenectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraparotid lymph nodes</td>
<td>Parotidectomy (superficial rather than complete when possible) + modified cervical dissection</td>
</tr>
<tr>
<td>Cervical lymph nodes</td>
<td>One-sided dissection of cervical nodes</td>
</tr>
<tr>
<td>Axillary lymph nodes</td>
<td>Axillary block dissection</td>
</tr>
<tr>
<td>Inguinal lymph nodes</td>
<td>Inguinal dissection. The iliac nodes (superficial and/or deep) may be included after taking into account the radiographic image and the opinion of the committee</td>
</tr>
<tr>
<td>Lymph nodes located outside the standard groups (popliteal, cubital, posterior triangle lymph node, etc.)</td>
<td>Complete nodal dissection as far as possible</td>
</tr>
</tbody>
</table>

### Table 5  Recommended Increased Safety Margins After Simple Excision According to the Breslow Depth of the Primary Tumor

<table>
<thead>
<tr>
<th>Breslow Depth</th>
<th>Recommended Lateral Margins, cm</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>≤1 mm</td>
<td>1</td>
<td>2 cm where feasible depending on the site</td>
</tr>
<tr>
<td>1-2 mm</td>
<td>1</td>
<td>3 cm in some hospitals</td>
</tr>
<tr>
<td>2.01-4.00 mm</td>
<td>2</td>
<td>3 cm in some hospitals</td>
</tr>
<tr>
<td>&gt; 4.00 mm</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6  Recommended Type of Lymphadenectomy Depending on the Site of the Metastatic Nodes
Available Adjuvant Treatments

Adjuvant Radiotherapy

Radiation therapy of the affected parts of the lymphatic system (after lymphadenectomy) reduces the likelihood of nodal recurrence by 20%-50% in some groups of patients with stage III disease who are considered high risk.\textsuperscript{73-75} It is therefore contemplated in the following cases:

1. Lymph node recurrence (irrespective of the prior clinical and pathologic staging of the case)
2. Lymph node metastasis with extracapsular spread in the histopathologic study.
3. Metastases in more than 3 nodes in the same lymph node chain
4. Lymph node macrometastasis (1 or more clinically enlarged lymph nodes of $>3$ cm in diameter)\textsuperscript{73}

If the patient is a candidate for interferon treatment, radiation therapy should be completed before this is started to avoid any risk of demyelination.\textsuperscript{76}

Interferon-\(\alpha\)

Adjuvant Therapy with High-Dose Interferon-\(\alpha\)

Adjuvant high-dose interferon-\(\alpha\)-2b has been shown to improve disease-free survival and also, albeit only in some studies, overall survival.\textsuperscript{77-88} The approved indications in Spain for high-dose interferon therapy are situations involving melanoma with a high risk of recurrence. It is, therefore, indicated in the following cases:

1. Patients with regional node metastases, in-transit metastases, or satellite metastasis who are disease free after surgery (stage III)
2. Patients with an ulcerated primary tumor (or local recurrence) greater than 2 mm (stage IIIB) or a lesion greater than 4 mm (stages IIB-IIIC)

However, because of the high toxicity of this therapy (see the Summary of Product Characteristics) the clinician must always evaluate the patient’s age and disease status and exclude pregnant women and patients with concomitant disease, a second neoplasm, or evidence of distant metastasis.\textsuperscript{88} Early start of treatment is recommended following a diagnosis of melanoma (within 8 weeks of diagnosis or the definitive surgical intervention). The 2-phase treatment regimen approved for high-dose interferon (known as the Kirkwood Schema) starts with an initial induction phase involving the administration of a higher dose (20 MU/m\(^2\)) administered intravenously 5 times a week for 4 weeks followed by a lower maintenance dose (10MU/m\(^2\)) administered subcutaneously 3 times a week for 48 weeks. The aim of treatment is to maintain the highest dose tolerated by the patient, but the dose may have to be adjusted depending on toxicity (see Summary of Product Characteristics). Before starting treatment, a general blood workup should be obtained including thyroid hormones, complete liver function and lipid tests, and hepatitis B and C serology. Patients should have an electrocardiogram, and some hospitals also recommend prior examination of the ocular fundus. Laboratory tests should be performed weekly to monitor toxicity during the induction phase and, depending on tolerance, monthly or bimonthly thereafter.

PEGylated Interferon-\(\alpha\)-2b

PEGylated interferon-\(\alpha\)-2b has been shown to have an efficacy similar to that of conventional interferon-\(\alpha\)-2b in the treatment of the various diseases for which the latter is indicated (melanoma and chronic hepatitis caused by the hepatitis C virus) and it offers a more comfortable dosage regimen and lower toxicity. This in turn facilitates longer treatment regimens than those currently used and the possibility of prolonging the benefits of interferon treatment (the disease-free period). Although the use of PEGylated interferon-\(\alpha\)-2b is currently only approved in the treatment of chronic hepatitis caused by the hepatitis C virus, it is expected that healthcare authorities will also approve it for patients with melanoma.\textsuperscript{87}

Other Adjuvant Treatments

Adjuvant treatments other than interferon-\(\alpha\)-2b should only be used in the context of a clinical trial. Currently, these alternatives are based on cell immunotherapy and the use of targeted agents, such as anti-cytotoxic T-lymphocyte antigen-4 antibodies.

Treatment of Patients with Metastatic Melanoma

Whenever possible, patients with metastatic disease should be included in clinical trials. The best candidates for systemic palliative treatment are patients in good general health with low tumor load. When a patient does not fulfill the criteria for enrolment in a clinical trial, other alternatives may be considered, including no treatment and symptomatic treatment, given the scant efficacy of palliative treatment in stage IV melanoma.

Surgery of Metastasis

Complete surgical resection is the only treatment for metastatic melanoma consistently associated with an improvement in 5-year survival. While it is not considered curative, surgical resection of metastases does prolong the patient’s survival.\textsuperscript{89} Surgical excision of metastasis should be considered for single lesions located in soft tissues, nonregional lymph nodes,\textsuperscript{90} the lung,\textsuperscript{90} and/or in selected cases when metastasis affects the central nervous system (see below) or digestive tract (especially in the case of bleeding metastases).\textsuperscript{91} Surgery should only be performed...
in patients in good general health and when the foreseeable disease-free interval is long and the growth of the lesions is not rapid.

**Palliative Radiation Therapy**

The indications for radiation therapy in metastatic melanoma include the following:

1. Multiple inoperable subcutaneous metastases
2. Single metastasis occurring after excision
3. Local recurrence of the primary tumor, visceral metastases (bone with spinal cord compression, multiple cerebral lesions), or inoperable lymph node involvement

The dose and fractionation of radiation therapy will vary mainly according to the site of the tumor, the foreseeable risk of complications, and the aim of treatment (radical, complementary, or palliative). Whenever possible, a hypofractionated treatment regimen should be used. In the case of brain metastases, holocranial radiotherapy, surgery, and radiosurgery should be considered depending on the clinical situation. Surgery followed by holocranial radiotherapy is the first-line treatment for patients with a single metastasis greater than 3 cm, a marked mass effect, and disease controlled on other levels. Radiosurgery is a therapeutic option in the case of a single metastasis with a diameter of less than 3 cm. The standard treatment for multiple metastases is radiation therapy with or without chemotherapy, but the benefits of prior radiosurgery in selected patients with 2 or 3 metastases should not be ruled out.

**Regional Hyperthermic Perfusion with Cytostatic Agents in the Treatment of Malignant Melanoma of the Limbs**

Isolated limb perfusion with cytostatic agents is indicated in patients with local recurrence or in-transit metastasis disseminated throughout a limb following the extirpation of at least 1 lesion when disease is localized within the limb. The drug combination that appears to be most effective in regional perfusion is melphalan plus tumor necrosis factor α. Moreover,

**Chemotherapy**

In view of the poor results obtained with chemotherapy in patients with stage IV MM (no chemotherapy regimen has significantly improved survival in this group), phase II trials of new drugs are justified, even as first-line treatments. The chemotherapy treatment regimens currently most recommended are those that include dacarbazine. Except in the context of experimental protocols, dacarbazine is considered to be the standard chemotherapy agent and it is approved by the health authorities. Dacarbazine has been shown to achieve a 10.2% to 20% response in phase III trials.

**Temozolomide**

Temozolomide has demonstrated efficacy similar to that of dacarbazine in phase III trials (clinical response rate of 13%). It is used particularly when an oral regimen is preferable and is prescribed in the context of compassionate use programs since its use has not been approved by the regulatory agencies. The advantage of this agent is that it crosses the blood-brain barrier, and so could reduce the risk of recurrence in the central nervous system.

**Fotemustine**

Fotemustine, an agent approved for the treatment of patients with melanoma, has been shown in randomized controlled trials to have some benefit over dacarbazine and furthermore it can be used to treat patients with brain metastases. This drug can be considered for first- or second-line use depending on the presence of brain metastases. The chief adverse effect is myelotoxicity.

**Polychemotherapy**

Combination chemotherapy regimens (cisplatin + vinblastine + dacarbazine [CVD], cisplatin + carmustine + vinblastine + dacarbazine [CBVD], and cisplatin/dacarbazine) have in general been shown to be associated with higher response rates than dacarbazine alone in phase II trials, but have not been shown to be superior with respect to single-agent therapy with dacarbazine in phase III trials. Moreover, because they are associated with increased toxicity, these regimens are not recommended for routine treatment. At this time, the combination that has been shown to obtain the highest rate of overall responses in a number of studies is dacarbazine + carmustine + cisplatin + tamoxifen, although this regimen has also failed to demonstrate improved survival in phase III trials.

**Immunotherapy**

**Single-Agent Interleukin-2**

Intravenous infusion of high doses of interleukin-2 is associated with a 15% response rate, with complete responses in one third of these patients. Of these complete responses, 70% are durable and, in some cases, represent a cure. However, the high toxicity of this regimen (with deaths from toxicity in around 0.5%-2% of patients) makes close management in an intensive care unit essential, and this type of care is only available in highly specialized hospitals serving a large number of patients. Owing to its high toxicity and the lack of any comparative studies with dacarbazine and/or polychemotherapy regimens, treatment with interleukin-2 has not yet been approved by the European regulatory agencies.

**Interferon-α**

Single-agent therapy with interferon-α, which has not been approved in the treatment of metastatic melanoma, has obtained a 10% to 15% response rate in phase I and phase II trials, but has not yet been compared with DTIC or polychemotherapy. Neither the addition of this agent to chemotherapy regimens (single-agent dacarbazine,
dactarbazine-cisplatin-tamoxifen, or CBVD) nor its use in combination with interleukin-2 has shown any significant benefit in phase III trials. Consequently, its use is not recommended outside of the clinical trial setting.

Vaccines

Phase II trials are currently underway in our region using heterologous cell vaccines and autologous dendritic cells pulsed with heterologous or autologous tumor. These may benefit some patients with small tumor masses or slowly progressing disease.

Biochemotherapy

The term biochemotherapy refers to regimens that combine dacarbazine and/or polychemotherapy with interferon-α (subcutaneous) or interleukin-2 (intravenous or subcutaneous) at variable doses. These treatment regimens are associated with high response rates (33%-64%) and considerable toxicity in phase II trials. However, since no phase III study has to date been published that shows a significant benefit over chemotherapy in terms of either disease progression or survival, the routine use of biochemotherapy cannot be recommended.

Other Treatments

There are several phase II and a few phase III trials currently underway with the goal of establishing the role of new treatments for metastatic melanoma. The treatments investigated in these trials range from immunotherapeutic agents to targeted therapies (for example, sorafenib, oblimersen, paclitaxel, and anti-CTLA-4 antibodies). The use of these treatments outside of the clinical trial setting is currently not justified.

Follow-up of Patients with Melanoma

The objective of follow-up in patients diagnosed with MM, as in other neoplastic diseases, is twofold. The first goal is the diagnosis of recurrence (local, regional, or distant) through the additional investigations and tests appropriate to the natural history of the process. The second aim is early diagnosis of a second melanoma. The simplest and most efficient methods should be used, and these may vary from one hospital to another. Prompt diagnosis is essentially justified if there is a possibility of effective rescue treatment. However, to date regular follow-up of these patients has not been shown to increase survival.

Although there is no consensus on which additional investigations should be considered routine practice, there is nonetheless general agreement that the use of such investigations should be guided in each case by prognostic factors and, especially, clinical and pathologic staging.

The following should be included at each patient visit: an update of the patient’s medical history designed to detect the signs and symptoms indicative of recurrence; a detailed examination of all areas of the skin; palpation of regional nodal basins or—depending on its availability in the hospital and the characteristics of the patient (for example in obese patients)—ultrasound assessment of the affected nodal basins. In addition, all patients should receive instruction on how to carry out a monthly self-examination and implement effective photoprotection. The patient looks for changes in pigmented macular lesions and monitors the appearance of any change in superficial lymph nodes. The hospital should also have a fast track system that affords these patients rapid access to a specialist if any unexplained signs or symptoms arise so that they do not have to wait for a routine visit.

Follow-up visits should be scheduled for a period of at least 5 years for patients in stages 0 and IA and for at least 10 years in patients with disease at more advanced stages. Because of the risk of a second melanoma, lifetime surveillance is necessary in patients diagnosed with MM (regardless of stage) who have a family history of melanoma or who have other suspicious lesions (clinically atypical nevi). The clinical follow-up regimens used in different hospitals can be summarized as follows:

1. Melanoma in situ. Annual follow-up for 3 to 5 years, without further investigations
2. Low-risk melanoma (stage IA). Follow-up for 5 to 10 years. Schedule: every 3 to 6 months for the first 2 years and every 6 months for the following 3 years (further follow-up, when necessary, is annual). Standard blood workup + LDH: 6-monthly to annual for the first 2 years and annually for the following 2 years. Chest radiograph with optional abdominal ultrasound annually for the first 5 years
3. Intermediate-risk melanoma (stages IB and IIA). Follow-up for 10 years. Schedule: every 3 to 6 months for the first 3 years, twice yearly for the next 2 years, and annually for the last 5 years. Standard blood workup + LDH 2 to 4 times a year for the first 3 years, then twice yearly for 2 years, and annually during the last 5 years. Chest radiograph with optional abdominal ultrasound twice a year for the first 3 years, annually for the following 2, and chest radiography only for the last 5 years
4. High-risk melanoma (stages IIB, IIC, and III). Follow-up for 10 years. Schedule: every 3 to 4 months for the first 3 years, twice yearly for the next 2 years, and annually for the last 5 years. Standard blood workup + LDH 2 to 4 times a year for the first 3 years, then twice yearly for 2 years, and annually during the last 5 years. Chest and abdominal CT (or chest radiograph with abdominal ultrasound in stages IIB and IIC) once or twice yearly for the first 3 years, annually for the following 2 years (not required during the last 5 years of surveillance)

Some hospitals also perform a scintigraphic bone scan and a cranial brain MRI scan (more sensitive) or cranial CT annually in patients in high-risk stages.

In addition to LDH, Other optional markers that may be monitored are tyrosinase, S-100β (a 50% increment in S-100β) is highly indicative of disseminated disease, although this test is currently only performed in clinical trials. Other additional examinations are ordered depending on clinical findings and laboratory test results.
Melanoma of Unknown Primary Origin

Melanoma of unknown primary origin is defined as the presence of metastases of melanoma (confirmed by histology) in the lymph nodes or in subcutaneous or visceral sites without evidence of a primary lesion; these cases represent between 2% and 6% of all melanoma patients.113-116 The prognosis in these patients does not differ substantially from that of patients with primary melanomas diagnosed at a similar AJCC stage.118 Although the strictest definition excludes cases with a history of excision of a probably melanocytic lesion without histologic confirmation, the clinical approach for this subgroup of patients does not differ from that used in patients with melanoma of unknown primary origin in the strict sense. In all patients diagnosed with metastatic melanoma without a known primary tumor, a series of examinations should be undertaken to rule out a noncutaneous melanoma, which is often not clinically evident. These should include complete examination of the skin and mucous membranes with particular attention to affected nodal basins (when applicable) and to less accessible areas, such as the genitals and scalp. Otolaryngologic, ophthalmologic, gynecologic, and digestive tract (gastroscopy and colonoscopy) examinations must also be performed.117 The AJCC staging system is used in this group of patients; disease is considered to be stage III if there is localized metastases to the skin and subcutaneous tissue and stage IV when there is visceral metastasis.20 Additional examinations are indicated to provide data for initial staging depending on the AJCC stage and the clinical signs; these do not differ from those used in patients with a known primary melanoma.117,118 The treatment of patients with melanoma of unknown primary origin should be determined on the basis of the same criteria used to determine optimum treatment in patients with a known primary cutaneous melanoma. When feasible, radical excision of the initial lesion or lesions is the first line treatment.119

Conflict of Interest

The authors declare no conflicts of interest.

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