ABSTRACT
Advanced melanoma is a disease with a poor prognosis. Most of the currently available chemotherapy agents are ineffective. In contrast to other cancers, immune-based and novel, targeted therapies appear to have some effect in melanoma. Exciting research in the past few years holds hope for the future. We provide an overview of the current management principles of this condition with special emphasis on the emerging options in the systemic therapy of advanced disease.

INTRODUCTION
The incidence of melanoma in western countries has been increasing rapidly over the past few decades—from 1 in 1500 in 1935 to 1 in 68 in 2002. Australia has the highest incidence of melanoma, (age-adjusted rate [AAR] 40.5 per 100 000 population), whereas India has one of the lowest AARs (0.2 per 100 000 population). It is possible that melanomas are under-reported in India, as many patients present with pigmented lesions of the skin in the early stages of the disease, who may be treated by dermatologists or general surgeons.

Notable risk factors for melanomas are white race and a tendency for developing sunburn, which could explain why Indians have a lower incidence. Exposure to the ultraviolet B (UV-B) component of the sun’s rays has been implicated in the aetiology of melanoma. A family history is present in 10%–15% of cases. Other risk factors include a history of prior melanoma, multiple atypical moles or dysplastic nevi, and certain inherited mutations.

A majority of melanomas present with early-stage disease, but a major proportion can present with loco-regionally advanced or metastatic disease. The clinical subtypes of melanoma have been described and they vary in their mode of presentation and final prognosis (Table I).

The few therapeutic options available for advanced melanoma have limited (interferon) or no effect (dacarbazine, interleukin-2) on survival. ‘Positive’ phase 3 clinical trials in advanced melanoma have not been conducted so far. We discuss the principles of management of melanoma and focus on the recent developments in the management of advanced disease.

PROGNOSTIC FACTORS AND STAGING
The depth of invasion is the most important prognostic factor of the primary tumour in melanoma (incorporated in the T stage of the TNM system), and traditional classification systems, such as Clark level and Breslow system, exploit this fact. The TNM stage is the most important prognostic factor (Table II). Ulceration increases the T stage by one level and generally indicates an adverse prognosis. The other important factors include age, growth pattern (superficial versus nodular), lymphovascular invasion, specific body sites (head and neck and acral melanomas have a poor prognosis), mitosis rate, negative versus positive margins of resection, impalpable versus clinically palpable regional lymph nodes, size and location of tumour in sentinel lymph nodes, extracapsular extension of the tumour in the lymph nodes, and site and size of metastases (skin-only metastasis has a better prognosis than visceral metastasis).

MANAGEMENT OF MELANOMA: AN OVERVIEW
For purposes of management, melanoma can be broadly classified as localized (stages I and II), locally advanced (stage III, lymph node involvement, satellite lesions or in-transit metastasis), and metastatic melanoma (Table III and Fig. 1). The prognosis differs widely, with survival in excess of 80% in the early stages and <10% with advanced melanomas.

Localized melanoma
These are treated by wide local excision with appropriate margins; adjuvant therapy with high-dose interferon (HDI) may be
**Table II. TNM staging of melanoma** (indicating the pathological stage)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>T stage (depth of invasion)</th>
<th>N stage (lymph node involvement or satellite lesions)</th>
<th>M stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Melanoma in situ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>≤1 mm with no ulceration, Clarke level II or III</td>
<td>N0 No regional LN metastasis</td>
<td>N1a 1 LN, clinically undetectable</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>≤1 mm with ulceration, or Clarke level IV or V</td>
<td>N1b 1 LN, clinically detectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>1.01–2 mm, no ulceration</td>
<td>N2a 2–3 LN, clinically undetectable</td>
<td>N2b No LN, in-transit or satellite lesions</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>1.01–2 mm with ulceration</td>
<td>N2c All other metastases with normal LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>2.01–4 mm, no ulceration</td>
<td>N3 4 or more metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) with metastatic nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>2.01–4 mm with ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>&gt;4 mm, no ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>&gt;4 mm with ulceration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDH lactate dehydrogenase  LN lymph node

**Table III. Pathological stage grouping, prognosis and broad management principles**

<table>
<thead>
<tr>
<th>Stages I and II</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized melanoma</td>
<td>Locally advanced melanoma</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
<td>5YS (%)</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>--------</td>
</tr>
<tr>
<td>0</td>
<td>pTis N0 M0  &gt;99</td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>pT1a N0 M0  95</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>pT1b N0 M0  89</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>pT2b-pT3a N0 M0  77–79</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>pT3b-pT4a N0 M0  63–67</td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>pT4b N0 M0  45</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Intent:** Curative  
**Local site:** Wide local excision of primary with appropriate margins +/- sentinel or complete lymph node dissection  
**Adjuvant therapy:** Consider HDI for T3b and T4

**Stage I and II Localized Melanoma**
- Surgery
- +/- Sentinel LN
- Consider HDI (T3b and T4)

**Stage III Locally Advanced Melanoma**
- Surgery
- LN Dissection
- Consider Adjuvant RT
- Consider HDI

**Stage IV Distal Metastasis**
- High Dose IL-2
- Chemotherapy
- Experimental

**Fig 1. Management of melanoma: An overview**
- LN lymph node  
- HDI high-dose interferon
considered in deeply infiltrating or ulcerated lesions (T3b and T4).10

Regional disease
Whenever feasible, regional disease is resected with the intent to
cure. Adjuvant therapy is given because of the high chance of
local and systemic relapse of regional melanomas.10 Unresectable
regional disease is treated systemically, chiefly for palliation. In
some cases, surgery may be possible after systemic therapy.
Radiotherapy has a limited role in regional disease; while improving
local control it does not affect the overall survival. A recent trial
comparing regional radiotherapy versus observation in localized
melanoma after regional lymphadenectomy did not show a survival
advantage for adjuvant radiotherapy.11 Systemic therapy for
melanoma might be useful in the adjuvant setting in resected
deeply infiltrating or ‘thick’ melanomas, and in melanomas with
regional spread.

Metastatic melanoma
Systemic therapy is administered for metastatic melanomas with
palliative intent. The role of surgery is well defined in metastatic
melanoma12 (Table IV). Surgery with curative intent is possible in
some cases, such as solitary metastases in the lung, liver or brain.
The currently available systemic therapy for metastatic melanoma
has a curative potential of <10% and hence consideration must be
given to the possibility of surgical resection of metastasis wherever
feasible.

**SYSTEMIC THERAPY**

**Adjuvant setting**
Deep and regionally advanced melanomas have long term survival
ranging from 30% to 70% (Table III). Many of these recur after surgery alone and might benefit from some form of adjuvant
therapy.

Chemotherapy as adjuvant therapy in melanoma. Extrapolating
from the response to chemotherapeutic agents when tried in the
metastatic setting, drugs, such as dacarbazine, cisplatin,
temozolomide and taxanes, have been tried as single agents or in
combination in resected melanomas. Unfortunately, no drug has
been beneficial in this setting.13,14

**High-dose interferon (HDI).** HDI was tried in phase 2 trials of
patients with metastatic melanoma and was found to be active,
prompting trials in the adjuvant setting. Interferon acts by direct
anti-proliferative and cytotoxic effects, potentiation of NK-, T-
and B-cell responses, and induction of autoimmunity.15 The first
randomized trial (E1684) demonstrated an absolute 1-year survival
difference between the interferon and placebo arms.16 Subsequent
phase 3 trials, though demonstrating disease-free survival
advantage with HDI, have not shown a benefit in overall survival
(Table V).17–23 Combined analyses of the Eastern Cooperative
Oncology Group (ECOG) trials showed that HDI therapy provides
improvement in relapse-free survival for patients with high risk
disease.18,19 Similarly, subgroup analysis from the European
Organization for Research and Treatment of Cancer (EORTC)
trials20,21 have suggested benefits restricted to high risk categories
(Iib-III and ulcerated melanomas).22

The appropriate post-surgical management strategies for stage
Iib-III melanoma include enrolment in a clinical trial, HDI, or
observation and follow up alone.24 Thus, after discussing the costs
and benefits of adjuvant HDI, it may be offered to selected
patients with stage Iib-III melanoma who have no serious co-
морbid conditions and have a good performance status.8,10

The toxicity of HDI can be significant, with up to 67% of
patients experiencing some grade III/IV side-effects. The
commonly experienced problems are flu-like syndromes,
myelosuppression, especially thrombocytopenia, hepatotoxicity,
and neuropsychiatric problems, including suicidal ideations and
depression.16,17,23 Efforts to decrease the dose, and hence the side-
effects of this treatment, have been unsuccessful. The other
limiting factor is the cost of therapy (Rs 500 000–1 000 000 for

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**Table IV. Role of surgery in metastatic melanoma**

<table>
<thead>
<tr>
<th>Benefit of surgery is clear</th>
<th>Benefit of surgery is likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia due to occult bleeding from intestinal metastasis</td>
<td></td>
</tr>
<tr>
<td>Bowel obstruction due to small bowel metastasis</td>
<td></td>
</tr>
<tr>
<td>Cutaneous or subcutaneous metastasis or metastases with ulceration, pain or impending ulceration</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis with neurological symptoms</td>
<td></td>
</tr>
<tr>
<td>Symptomatic brain metastasis</td>
<td></td>
</tr>
<tr>
<td>Life-threatening haemorrhage from metastasis</td>
<td></td>
</tr>
<tr>
<td>Solitary asymptomatic visceral metastasis resectable with minimal morbidity</td>
<td></td>
</tr>
<tr>
<td>Bone metastasis with pain or joint involvement, non-responsive to radiation</td>
<td></td>
</tr>
<tr>
<td>Solitary brain metastasis without symptoms</td>
<td></td>
</tr>
<tr>
<td>Large nodal metastasis in the absence of symptoms and with concurrent low-volume systemic disease</td>
<td></td>
</tr>
<tr>
<td>Extensive skin and soft tissue metastases in the absence of visceral metastases</td>
<td></td>
</tr>
<tr>
<td>Isolated growing metastasis in the setting of stable or regressing metastases after systemic therapy</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Slingluff et al.12

---

**Table V. Trials of adjuvant high-dose interferon in melanoma**

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Treatment arms</th>
<th>Stage</th>
<th>Chief findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 168416</td>
<td>280</td>
<td>HDI for 1 year and Observation</td>
<td>Iib or III</td>
<td>HDI improved both RFS and OS</td>
</tr>
<tr>
<td>ECOG 16907</td>
<td>642</td>
<td>HDI for 1–2 years and Observation</td>
<td>Iib or III</td>
<td>HDI improved RFS but not OS</td>
</tr>
<tr>
<td>EORTC 1895220</td>
<td>1388</td>
<td>HDI for 1–2 years and Observation</td>
<td>Iib or III</td>
<td>HDI for 2 years improved RFS but not OS. No benefit in RFS or OS in the 1-year arm</td>
</tr>
<tr>
<td>EORTC 1899121</td>
<td>1256</td>
<td>HDI (peg-interferon) for 5 years and observation</td>
<td>III</td>
<td>HDI improved RFS but not OS</td>
</tr>
<tr>
<td>Sunbelt Melanoma Trial23</td>
<td>774</td>
<td>HDI ± CLND and observation for positive SLNB</td>
<td>III</td>
<td>No benefit of HDI in those with a single positive lymph node</td>
</tr>
<tr>
<td>HDI high-dose interferon</td>
<td>RFS relapse-free survival</td>
<td>CLND completion lymph node dissection</td>
<td>OS overall survival</td>
<td>SLNB sentinel lymph node biopsy</td>
</tr>
</tbody>
</table>
1-year), which can be prohibitive in resource-limited countries, such as India.

A recent publication comparing the use of induction interferon for 1 month with 1 year of adjuvant interferon found no significant difference between these 2 schedules.\textsuperscript{25} Although this trial used inadequate doses of interferon in the standard arm, the use of the 1-month schedule could save costs and decrease side-effects. This thought-provoking concept is currently being explored in a multicentre randomized trial (ECOG 1697; \url{www.clinicaltrials.gov} ID: NCT00003641).

Other agents. Various combinations of chemotherapy and interferons and interleukins (biochemotherapy) have been tried on melanomas, but without much success. Adjuvant granulocyte–monocyte colony stimulating factor was found to be useful in phase 2 trials; the results of phase 3 trials are awaited.\textsuperscript{36,27}

Metastatic setting: Chemotherapy, immunotherapy and ‘targeted’ therapy

Chemotherapy. Chemotherapy with single-agent dacarbazine or temozolomide is often used in metastatic melanoma in both the clinic and in the trial setting as the comparator arm. Unfortunately, neither dacarbazine nor temozolomide have been tested against a placebo and been proven to be superior.

The initial demonstration that the tumours respond to many of the conventional chemotherapeutic agents has been the basis for trials that have used several of these agents in combination with each other and with interferon and interleukin. None of the agents have shown a clear advantage and despite 3 decades of research, the median survival in patients with disseminated disease continues to remain a disappointing 8–9 months in the most recent phase 3 trials (Table VI).\textsuperscript{26–34}

**Immunotherapy and the limited success of interleukin-2.** High-dose interleukin-2 (IL-2) is the only therapy which has shown benefit in advanced metastatic melanoma.\textsuperscript{35–37} Its unique feature is the dosing, which is done ‘to tolerance’, i.e. a high dose of 600 000–720 000 IU/kg is administered every 8 hours (maximum of 14 doses) until grade III/IV side-effects occur. The side-effects include capillary leak syndrome causing severe hypotension, which requires inotropic support, fever with chills, dyspnoea, weight gain and oliguria—which may even lead to early mortality in some patients. Intensive care unit monitoring may be required in patients who develop haemodynamic and pulmonary complications. Studies have suggested a definite learning curve, with outcomes improving in centres with more experience.\textsuperscript{38}

IL-2 therapy had a 16% response rate (6% complete and 10% partial) with >80% complete responders having excellent long term outcomes and even cure.\textsuperscript{35} The drawback of this treatment was the lack of overall survival benefit for the entire cohort of patients who were treated; only a small subset of patients (who cannot be identified prospectively) benefit. The responses are best in those with only cutaneous metastasis\textsuperscript{39} compared with other sites. The high cost (estimated cost of the drug alone is approximately Rs 500 000–700 000 for the entire course) and the high toxicity means that this type of therapy is out of the reach of most patients in India. The alternative patterns of administration of IL-2 (subcutaneous, lower doses with or without interferons), though less toxic, have not been shown to be efficacious.

Biochemotherapy. Considering the toxicity of higher doses of interferon and IL-2, modified doses of both were tried in combination with various chemotherapeutic agents. Although the response rates were higher in all these trials compared with single agent chemotheraphy or immunotherapy alone, no phase 3 trial has demonstrated a disease-free or overall survival advantage.\textsuperscript{36–38}

Both chemotherapy and biochemotherapy results have been disappointing. The only therapy that works is high-dose IL-2, but it benefits <10% of the patients and is limited by cost and toxicity issues. Thus, it can be considered only in a few patients selected on the basis of age, absence of co-existing medical conditions, and absent or controlled brain metastases.\textsuperscript{39} Hence, recent research has focused on novel drugs.

**NOVEL AND TARGETED THERAPY**

**B-Raf inhibitors**

The single most important molecular alteration in melanoma is in the B-Raf protein, which is involved in downstream signalling of the ras-raf-mek pathway.\textsuperscript{40} This protein is activated in 50%–65% of all melanomas. However, studies with sorafenib (a B-raf inhibitor) as a second-line agent have been disappointing.\textsuperscript{41} More recent studies with PLX4032, a selective inhibitor of the oncogenic V600E mutation in the B-Raf kinase, have shown promise. Five of seven patients with B-Ref V600E+ showed a response in a phase 1 study.\textsuperscript{42}

**Imatinib and dasatinib**

The molecular target of imatinib is C-kit, which is activated in 30% of acral lentiginous and mucosal melanomas. Because of the success of imatinib in targeting these melanomas in a small groups of patients\textsuperscript{43} (3% of all melanomas), imatinib or dasatinib could play a key role in their treatment.\textsuperscript{44,45}

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**Table VI.** Chemotherapy and biochemotherapy trials in metastatic melanoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Treatment arms</th>
<th>Chief findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middleton et al.\textsuperscript{24}</td>
<td>305</td>
<td>Temozolomide v. DTIC</td>
<td>Median survival 7.7 months for temozolomide and 6.4 months for DTIC</td>
</tr>
<tr>
<td>Legha et al.\textsuperscript{26}</td>
<td>52</td>
<td>CVD chemotherapy (cisplatin, vinblastine and DTIC)</td>
<td>Overall response rate 40% (2 patients had complete response), median survival was 12 months</td>
</tr>
<tr>
<td>Luikart et al.\textsuperscript{27}</td>
<td>57</td>
<td>DTIC v. Vincristine, bleomycin, DTIC (VBD)</td>
<td>VBD was not superior to DTIC</td>
</tr>
<tr>
<td>Chapman et al.\textsuperscript{28}</td>
<td>240</td>
<td>DTIC v. Dartmouth regimen (DTIC, cisplatin, BCNU, tamoxifen)</td>
<td>Median survival 7 months, similar in both arms; response rate was slightly higher in combination arm (18.5% v. 10%)</td>
</tr>
<tr>
<td>Eton et al.\textsuperscript{29}</td>
<td>190</td>
<td>CVD alone v. CVD followed by IFN and IL-2</td>
<td>Improved response rate and PFS with biochemotherapy but no significant difference in OS</td>
</tr>
<tr>
<td>Atkins et al.\textsuperscript{30}</td>
<td>416</td>
<td>CVD alone v. CVD followed by IFN and IL-2</td>
<td>Biochemotherapy had an inferior PFS and OS</td>
</tr>
<tr>
<td>EORTC 18951\textsuperscript{31}</td>
<td>363</td>
<td>Cisplatin, DTIC and IFN alpha + high-dose IL-2 v. high-dose IL-2 alone</td>
<td>Improved responses but no difference in survival</td>
</tr>
</tbody>
</table>

OS overall survival  DTIC dacarbazine  BCNU carmustine  PFS progression-free survival
Anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) mediated therapy

CTLA-4 is expressed in activated T cells and suppresses their function and decreases autoimmunity and over activation of the immune system. Blocking this molecule leads to stimulation of the T cells whereby they could possibly mount anti-tumour immune responses. As a melanoma has exhibited responses to immune-based therapies, anti-CTLA-4 antibodies were tried as therapeutic agents. The autoimmune toxicities observed with anti-CTLA-4 antibodies include dermatitis, enterocolitis, hypophysitis, uveitis, hepatitis and nephritis. Ipilimumab and tremelimumab block the CTLA-4 molecule on the T-cell surface and have shown promising activity in phase 1 and 2 trials. However, a phase 3 trial of tremelimumab, in combination with interferon in stage III or IV melanomas, was disappointing, though a subset of patients benefited. A trial combining ipilimumab and dacarbazine (DTIC) versus DTIC alone has also been completed (www.clinicaltrials.gov ID:NCT00324155) and the results are likely to be available in 2010.

Adoptive immunotherapy and vaccines

Trials of vaccines in melanoma have been disappointing and some trials of vaccine-based therapy showed decreased survival (as in the GM2-KLH vaccine in E1694 and the EORTC 18961 trials). The first successful vaccine therapy for melanoma was presented at the American Society of Clinical Oncology (ASCO) 2009 meeting; a combination of IL-2 and a peptide vaccine showed significant improvement in response rates (22.1% vs. 9.7%) and progression-free survival (2.9 vs. 1.6 months). The median overall survival improved in the vaccine arm (17.6 vs. 12.8 months) with a trend towards significance (p=0.0964).

Another novel vaccine strategy is the introduction of tyrosinase DNA (tyrosinase being an enzyme expressed in melanoma cells) to stimulate cytotoxic T cells against melanoma cells. This has shown promise in a phase 1 study.

Anti-angiogenic therapy

Axitinib, a multi-targeted antagonist of vascular endothelial growth factor receptors (VEGFR-1, 2 and 3) demonstrated an impressive 19% response rate in highly pre-treated patients in a phase 2 study. Bevacizumab, a humanized monoclonal antibody inhibitor of the VEGF, was tried along with paclitaxel and carboplatin in a phase 2 trial and the combination showed improved progression and overall survival (BEAM trial) although the results were not statistically significant. Bevacizumab, a humanized monoclonal antibody inhibitor of the VEGF, was tried along with paclitaxel and carboplatin in a phase 2 trial and the combination showed improved progression and overall survival (BEAM trial) although the results were not statistically significant.

Anti-BCL2 antisense oligonucleotide

BCL2 is an anti-apoptotic molecule, which is overexpressed in melanoma cells and confers resistance to cell kill by various chemotherapeutic agents. Oblimersen sodium, an anti-BCL2 antisense oligonucleotide showed promising results in combination with DTIC in phase 2 trials. A phase 3 trial in combination with DTIC, however, did not demonstrate a statistically significant improvement in overall survival compared with DTIC alone (9.1 vs. 7.9 months), but response rates and progression-free survival improved. This demonstration of overall survival benefits in subgroups of patients with LDH values ≤2 times the upper limit of normal have prompted further studies of oblimersen in melanoma.

Other attempts at treatment of melanoma include strategies using molecules starting the Map-kinase, MEK pathways and the Ras pathway (farnesyl transferase inhibitors), and gene therapy using Allovectin-7 (a plasmid encoding HLA-B7 and beta-2 microglobulin, delivered intra-lesionally in a lipid system and thereby stimulating a localized inflammatory response). The latter has shown promise in a phase 2 trial and is currently undergoing phase 3 testing.

SUMMARY AND CONCLUSIONS

Table VII summarizes the various treatment approaches and their current status in the treatment of melanoma. At our institution, melanomas in early stages are managed with surgical resection. Radiotherapy is offered to all regionally advanced melanomas (positive lymph node metastasis). Interferons are not being used routinely. For metastatic disease, we use single-agent DTIC or temozolomide if the patients have a good performance status. For others, only supportive treatment is offered. High-dose IL-2 is offered in selected tertiary centres in India, but data on outcomes are not available.

Extensive research in the past 2 decades has not produced

| Table VII. Therapeutic approaches in melanoma and their current status |
|-----------------|------------------|------------------|
| Approach         | Status                                                      |
| Surgery          | Standard of care for early-stage disease. Has a definite role in advanced stages, including limited metastatic disease (Table IV). |
| Radiotherapy     | Helps in loco-regional control into lymph node disease metastatic but no impact on overall survival has been shown. Localized radiation may be used to palliate. |
| Interferon       | Adjuvant therapy with high-dose interferon improves disease-free survival in T3, T4 and lymph node metastatic disease; conflicting data on overall survival; no role for interferon in metastatic disease. |
| Interleukin-2    | High-dose IL-2 is the only therapy that has shown prolonged survival in metastatic melanoma; particular benefit in patients with disease metastatic to skin only. Limited by cost and high toxicity and the small number of patients who actually benefit (<10%). |
| Chemotherapy (single agent, combinations) | No survival benefit demonstrated with any chemotherapy-based options either in adjuvant or metastatic disease setting. Most active agents are DTIC and temozolomide. |
| Biochemotherapy  | Combinations of conventional chemotheraphy agents with IL-2 or IFN have higher response rates but none have demonstrated survival advantage in phase 3 trials. |
| Melanoma vaccine | All phase 3 trials, except one, have not shown benefit of vaccine-based approaches. |
| Targeted therapies | Novel drugs targeting the B-Raf pathway, c-kit pathway, CTLA-4 antibody, VEGFR have shown promise in phase 1 and 2 studies; hold promise for future treatment strategies in melanoma. |

DTIC dacarbazine  IL-2 interleukin-2  IFN interferon  CTLA cytotoxic T-lymphocyte associated  VEGFR vascular endothelial growth factor receptors
improved survivals in advanced melanoma, but there has been an exploration in knowledge on the biology of the disease. Multiple trials have exposed the futility of conventional chemotherapy. Immune therapy is effective but benefits a minority of patients. Targeted and novel therapeutic agents, painstakingly developed by extrapolation from molecular studies, hold promise for the future in tackling this disease.

REFERENCES


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