Subcutaneous metastases from melanoma: a discussion of clinical experience

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Practice points

- The majority of locoregional relapses of cutaneous melanoma occur in the form of intralymphatic dissemination as subcutaneous local recurrences or in-transit metastases. Stage IIIB/C subcutaneous metastases (SMs) are also a common type of distant metastasis (stage M1A).
- Treatment of SMs is challenging and it depends on the number, site, depth, size, clinical behavior and presence of metastases in other sites.
- Isolated, resectable SMs should be treated surgically with clear tissue margins. In the setting of single, resectable in-transit metastases, sentinel lymph node biopsies should be considered, even if the first draining lymphatic basin has been surgically explored for the primary tumor.
- In cases of multiple/unresectable lesions, several local modalities can be used in specific situations, such as carbon dioxide laser ablation, radiotherapy, cryotherapy, intralesional injections and electrochemotherapy.
- Hyperthermic isolated limb perfusion (HILP) is considered the preferred method of treating multiple or bulky and frequently recurrent in-transit metastases in the extremities, as it allows for treatment of the whole limb and the achievement of 20–50-times higher concentrations of cytotoxic agent (mainly melphalan) compared with systemic therapy. HILP can be performed with minimal locoregional toxicity (even in combination with TNF- α) and systemic leakage in specialized centers, allowing for high response rates and long-lasting remission.
- Regional chemotherapy can also be delivered in the form of isolated limb infusion.
- Electrochemotherapy is a simple and attractive method for the fast ablation of SMs of the limbs that are not feasible for HILP or isolated limb infusion, as well as cutaneous melanomas in nonextremity locations.
- The recent advances in the systemic therapy of metastatic melanoma, including immunotherapy (the anti-CTLA4 ipilimumab and anti-PD-1 molecules) and targeted therapy (with BRAF/MEK inhibitors; e.g., vemurafenib, dabrafenib and trametinib), have also had a significant impact on treatment modalities in SM. These new therapies offer significantly improved progression-free and overall survival for advanced melanoma patients, and targeted therapy in particular is characterized by high response rates, while immunotherapy with ipilimumab is related to long-term responses, mainly with low-burden and low-symptomatic disease.

SUMMARY The majority of locoregional relapses of cutaneous melanoma occur as subcutaneous local recurrences/in-transit metastases; subcutaneous metastases (SMs) are also common in distant metastases. SM therapy is challenging and depends on the number, site, depth, size, clinical behavior and presence of other metastases. Isolated, resectable SMs should be treated surgically. In multiple/unresectable lesions, several local modalities are used: carbon dioxide laser ablation, radiotherapy, cryotherapy, intralesional injections and

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SUMMARY (CONT.) electrochemotherapy. Hyperthermic isolated limb perfusion is the preferred method of treating multiple, bulky in-transit metastases in extremities, allowing for high response rates and long-lasting remission. Electrochemotherapy is a simple method for the fast ablation of SMs that are not feasible for hyperthermic isolated limb perfusion. Recent advances in systemic therapy of melanoma, including immunotherapy (anti-CTLA4/anti-PD-1) and targeted therapy (BRAF/MEK inhibitors), have significantly impacted on SM treatment. We present our own SM cases treated with different modalities. The future of SM therapy will rely on a combination of different local, locoregional and systemic modalities, and we can expect major improvements in long-term outcomes.

KEYWORDS

- electrochemotherapy
- in-transit metastases
- isolated limb perfusion
- local recurrence
- melanoma

The majority of locoregional relapses of cutaneous melanoma occur in the form of intralymphatic dissemination as subcutaneous local recurrences or in-transit metastases (SM/IT). However, this is not a single disease, but rather it represents a diverse pattern of failures with different clinical behaviors. The median time to appearance of in-transit metastases (ITs) ranges from 13 to 16 months, often preceding manifestation of systemic disease [1]. Intralymphatic ITs are designated as stage N2c (without regional nodal metastases) or N3 (with synchronous nodal metastases) according to the American Joint Committee on Cancer (AJCC) staging system, and are grouped together as stage IIIB/C [2]. Moreover, subcutaneous metastases (SMs) are another common type of distant metastases (stage M1a if they represent the only manifestation of systemic dissemination). It is a prognostically variable group of patients, with 5-year overall survival rates ranging from 69% in the N2c subgroup with relatively good outcomes to approximately 20% in the M1a subgroup [2]. While at the locoregional stage in-transit disease has a similar prognosis to advanced nodal metastases, it is more difficult in management. Treatment of SM is challenging and depends on the number, site, depth, size, clinical behavior and presence of metastases in other sites [1]. The method of therapy should be tailored to the extent of the subcutaneous disease, as well as the possible presence of metastases in other locations. Treatment options comprise local, regional and systemic modalities. Isolated, resectable SMs should be treated surgically with clear tissue margins. There is no need for wide excision. In the setting of single, resectable ITs, sentinel lymph node biopsies could be considered, even if the first draining lymphatic basin has been surgically explored for primary tumor [3]. In cases of multiple/unresectable lesions, several local modalities can be used in specific situations: carbon dioxide laser ablation, radiotherapy, cryotherapy, intralesional injections

and electrochemotherapy (ECT). New systemic therapies have been shown to offer significantly improved progression-free and overall survival in advanced melanoma patients, and they can be utilized in the treatment of SM/IT.

Surgical & ablation therapy

Resectable in-transit recurrences should be preferably treated surgically with clear margins (no excisional margins have proven to be beneficial), but amputation is not indicated and it does not improve survival. We typically utilize macroscopic margins of a few millimeters in size with primary closure. In case of the absence of previous lymph node dissections in the group of patients with first-time single IT recurrence, we consider nodal restaging with sentinel lymph node biopsy [4]. In case of recurring, indolent in-transit lesions, re-excision is possible if it is technically feasible. With the presence of numerous lesions, carbon dioxide laser ablation can be used, but the recurrence rate is very high, and this technique is limited to lesions of <1 cm in diameter [5]. Other local modalities, such as radiotherapy or cryotherapy, may be used in special situations.

Radiotherapy may be used as an adjuvant therapy after resection of local/IT recurrences (especially if marginal resection was performed), but also for palliation of the symptoms (e.g., pain or bleeding). A single institution review of palliative radiotherapy in advanced melanomas including 33 patients with IT reported a 77% response rate at this disease stage. In palliative therapy, fractionation is individualized, but we generally prefer short-term treatment, so high individual doses or hypofractionation is advisable [6]. According to recommendations, radiotherapy can also be utilized as an adjuvant treatment after resections of SM/IT [7].

Electrochemotherapy

ECT is a simple and attractive method for the fast ablation of SMs in the limbs that are not

feasible for hyperthermic isolated limb perfusion (HILP) or isolated limb infusion (ILI; see below), as well as SMs in nonextremity locations. ECT is a new method combining the administration of low-dose chemotherapeutic drugs that are poorly permeant to tumor cells and the application of electric pulses to tumors, facilitating drug delivery into the cells. ECT activity is based on this enhanced drug delivery, thereby potentiating chemotherapeutic drug activity (the drug's concentration inside tumor cells is 80–8000-times greater than after intravenous administration of cisplatin and bleomycin, respectively), and it does not affect the tissues that are not exposed to the electric pulses. Bleomycin can be administered either intravenously or intratumorally, while cisplatin can only be administered intraleSIONally. ECT utilizes established standard operating procedures from the European Standard Operating Procedures of Electrochemotherapy (ESOPE) [8]. Because the delivery of electrical pulses causes painful muscle contractions during treatment, the therapy is usually given under brief general anesthesia.

ECT has been proven in several Phase II and cohort studies to be a highly effective method (responses exceeding 90%) in the local treatment of cutaneous metastases (with size limits; [Table 1](#)). ECT is predominantly used in the treatment of multiple SMs when they cannot be excised due to their number or location. ECT is a simple-to-administer treatment that may improve quality of life in patients with metastatic disease, and clinicians should not hesitate to use it, even for elderly patients. Moreover, ECT can be repeated in cases of partial response (PR) or locoregional recurrence. An analysis of our data on ECT based on the administration of bleomycin 15 U/m² given intravenously 10 min before electroporation in 34 melanoma patients with SM/IT was presented during the *2nd International Users' Meeting* in Bologna, Italy, in 2013, confirming high local efficacy with PR/complete response (CR; 29 cases) or stable disease (four cases) observed in all except one case ([Figure 1](#)) [9]. In ulcerated ITs, recurrent bleeding ceased immediately after ECT. However, in a large percentage (50%) of patients, relatively fast locoregional progression (during the first 10 weeks after ECT) was observed in the form of the appearance of new lesions. Treated nodules usually do not recur in a previously treated area, which in our opinion may be related to ECT-induced fibrotic scarring. Seven patients

had repeated ECT for newly appeared lesions, and the tolerance was very good. Our results are concordant with previous studies and, in our opinion, this treatment modality plays an important role in the palliation of unresectable SMs due to high local efficacy and an increase of patients' quality of life due to decreased bleeding, ulceration, painful and disturbed everyday activities and superficial tumors, which cannot be treated with other techniques. It may have some curative effects in patients with slowly progressing tumors. However, it seems that this method as a sole treatment does not allow for long-term locoregional control in the majority of cases, nor does it improve the survival of patients in the advanced stages of melanoma. Further studies evaluating the role of this technique in the combined treatment of stage IV melanomas are necessary.

Isolated limb perfusion & ILI

HILP is considered to be the preferred method of treating multiple or bulky and frequently recurrent SM/IT in the extremities, as it allows for the treatment of the whole limb and the achievement 20–50-times higher concentrations of cytotoxic agent (mainly melphalan) compared with systemic therapy. Regional chemotherapy is combined with hyperthermia and administered through isolated and cannulated major vessels for 60–90 min ([Figure 2](#)). In bulky disease, melphalan is preferably combined with TNF- α , which has tumor-selective angiotoxic effects, antitumoral activity and increases the uptake of concomitant chemotherapeutics. Many studies have demonstrated the high efficacy of this procedure for the local control of extremity ITs ([Table 2](#)) [18–23]. A systematic review of 22 studies comprising 2018 melanoma patients with ITs demonstrated a median CR rate of 58% and an overall response rate (PR plus CR) of 90% [24]. The responses for melphalan in monotherapy were somewhat lower than when in combination with TNF- α (46 vs 69%, respectively). However, the only randomized trial of isolated limb perfusion with melphalan with or without TNF failed to show any significant differences in terms of the entire group [25]. The methodology of this study was criticized because clinical response was evaluated very early, after only 3 months, while the CR rate at 6 months suggested an improvement in the combination arm (42 vs 20%). The toxicity in the melphalan and TNF arm was higher. Similarly, a large single-institution analysis by

Table 1. Results of the major series including melanoma treated with electrochemotherapy.

Author (year)	Histological type of tumor	Patients (n)	Treated lesions (n)	Response on ECT, n (%)					Ref.
				PD	NC	PR	CR	OR	
Intravenous bleomycin									
Mir <i>et al.</i> (1998)	Melanoma	7	30	1 (3)	2 (7)	3 (10)	24 (80)	27 (90)	[10]
Quaglino <i>et al.</i> (2008)	Melanoma	14	233	17 (7.3)		80 (34.3)	136 (58.4)	216 (92.7)	[11]
Intravenous or intratumoral bleomycin									
Campana <i>et al.</i> (2009)	Melanoma, breast cancer, HN SCC	52	267	16 (6)		126 (47.2)	125 (46.8)	251 (94)	[12]
Matthiessen <i>et al.</i> (2011)	Melanoma, BCC, SCC, breast cancer	24	94	18 (19.2)		18 (19.2)	58 (61.6)	76 (80.8)	[13]
Intratumoral bleomycin									
Byrne <i>et al.</i> (2005)	Melanoma	21	52	5 (10)	10 (19)	4 (8)	33 (63)	37 (71)	[14]
Heller <i>et al.</i> (1998)	Melanoma, BCC, SCC, Kaposi's sarcoma	34	143	1 (0.7)		12 (8.4)	130 (90)	142 (99.3)	[15]
Intratumoral cisplatin									
Sersa <i>et al.</i> (2000)	Melanoma	14	211	16 (8)	24 (11)	23 (11)	148 (70)	171 (81)	[16]
BCC: Basal cell carcinoma; CR: Complete response; ECT: Electrochemotherapy; HN: Head and neck; NC: No change; OR: Overall response; PD: Progressive disease; PR: Partial response; SCC: Squamous cell carcinoma. Adapted from [17].									

Alexander *et al.* failed to show an improvement in terms of in-field progression-free survival with the addition of TNF [26]. On the other hand, the early reported results of one randomized trial revealed that the subgroup of patients with bulky melanoma had CR rates of 58% when on isolated limb perfusion with melphalan plus TNF plus interferon as compared with 19% on isolated limb perfusion with melphalan only [27]. These observations are supported by a nonrandomized series presented by Rossi *et al.*, demonstrating a 66.7% CR rate in a group of bulky melanomas treated with melphalan combined

with low-dose TNF as compared with a CR rate of 30% in a group treated with melphalan only [28]. According to one randomized study, prophylactic isolated limb perfusion after excision of symptomatic ITs did not show any impact on overall survival [29]. HILP can be performed with minimal locoregional toxicity (even in combination with TNF- α) and systemic leakage (monitored using a precordial scintillation probe for the detection of technetium-labeled albumins) in specialized centers, allowing for a high response rate and long-lasting remission. Lymph node dissection of the respective

Figure 1. Effect of electrochemotherapy in multiple bleeding subcutaneous local recurrences or in-transit metastases in the edematous lower extremity (initially and 6 weeks after electrochemotherapy).

nodal basin (if not removed earlier) is a part of the HILP procedure, meaning that it addresses all micrometastatic disease in the extremity, because the nodal metastases rate in the presence of SM/IT is as high as 50% [4,30]. The responses usually take 6–8 weeks to occur, but the median duration of response exceeds 20 months [31]. Although HILP with melphalan allows for the achievement of excellent responses in patients with advanced ITs, many patients will eventually experience systemic relapse of the disease. For the selection of this method of treatment, multiple factors should be taken into account, such as the patient's general condition (as this method demands good performance status due to long-lasting operations and expected morbidity), technical difficulties (e.g., after previous iliac–inguinal nodal dissection) and availability of equipment.

The minimally invasive technical variation of HILP is ILI, which was proposed by Australian investigators [32], with vessels cannulated percutaneously via contralateral femoral vessels. The cytotoxic agent is given in hyperthermic conditions, but without an oxygenator and for a shorter duration (30 min). This alternative procedure is a much less invasive technique than HILP; however, lower CR rates and shorter median durations of response have been observed for this technique [31]. The current authors have no experience with the ILI technique. Both techniques (HILP and ILI) can be repeated in selected cases. Iliac isolated limb perfusion has the advantage of treating the whole limb up to the groin; ILI only treats the surface to the upper third of the thigh. ILI is probably slightly less effective than isolated limb perfusion, but it is less invasive and easier to repeat.

Local immunotherapy

• Topical immunotherapy

Imiquimod stimulates the immune response by activating macrophages and other cells through binding to cell surface receptors, such as TLR7. This binding induces secretion of inflammatory cytokines, predominantly TNF- α , IL-1, -6, -8 and -12 and IFN- α , which in turn stimulate T cells, thereby enhancing innate and acquired cellular immunity [33,34]. It also has the potential to induce apoptosis of tumor cells and inhibit tumor-induced angiogenesis via IL-18 and IFN- γ [35,36]. Imiquimod is approved for the treatment of superficial basal cell carcinoma, actinic keratoses and anogenital warts. It may also be active

in invasive cutaneous melanoma. Since 2000, there have been several reports describing the complete and almost CR (>90%) of cutaneous melanoma ITs to imiquimod [37–42]. There is no consensus regarding the optimal treatment protocol. In published case studies, 5% imiquimod was applied from three-times weekly to twice daily for 8–68 weeks [37–40]. Therapy is generally well tolerated. The most common side effects are erythema, ulcerations, itching, burning and tenderness. The response of cutaneous metastatic melanoma to topical imiquimod is encouraging; however, it gives poorer responses in SMs in comparison to purely cutaneous lesions. This is probably related to the limited percutaneous penetration and different tumor biology of subcutaneous lesions [43,44].

• Intralesional immunotherapy

PV-10

Rose bengal is an intravenous diagnostic agent that undergoes rapid hepatic excretion in an unmetabolized form. PV-10 is a 10% solution of Rose bengal that is suitable for intralesional administration. PV-10 passes through the membrane of cancer cells and concentrates in lysosomes, triggering lysosomal release. Selective uptake of PV-10 by cancer cells results in necrosis in melanocytes without affecting normal dermal fibroblasts [44]. Tumor ablation by PV-10 leads to increased exposure of the tumor antigens to nearby antigen-presenting cells, facilitating the presentation of antigenic targets to T cells and B cells. Induction of a systemic antitumor immune response can mediate the regression of untreated nontarget lesions (bystander response) [45]. In a Phase II trial by Agarwala *et al.*, CR was achieved in 53% of the injected lesions [46,47]. A total of 25% of patients had CRs in the target lesions and 26% had PRs, giving an objective response rate of 51%. The locoregional disease control (CR + PR + stable disease) rate was 69%. Among the 42 subjects with bystander lesions, CR of the untreated lesions was reported in 26%, the objective response rate was 33% and locoregional control was observed in 50% of cases. Regression of bystander lesions strongly correlated with response in the target lesions. Adverse events were predominantly mild to moderate, with the most common being pain at the treatment site, vesicles or edema, followed by swelling, pruritus and skin discoloration [46,47]. The apparent safety of PV-10 treatment supports its use, particularly in older patients and those

Figure 2. The cannulated major femoral vessels for hyperthermic isolated limb perfusion of in-transit metastases limited to the lower extremity.

with comorbidities. Further studies using this agent are ongoing.

BCG

Originally developed as an attenuated agent for vaccination against TB, BCG has been found to nonspecifically augment the immune response to a variety of tumors. In 1974, Morton *et al.*

reported series of 151 patients treated by direct intralesional injections with BCG [48]. In total, 90% regressions of the injected melanoma nodules and 17% regressions of the uninjected lesions were observed. However, intralesional BCG treatment appears to be less safe than other local treatments. Disseminated intravascular coagulation, anaphylaxis and systemic BCG infection have been reported [49]. The doses used in patients who have not been previously sensitized to BCG are approximately 3×10^6 CFU/ml of Tice strain BCG, with approximately 0.1 cc administered to a typical dermal nodule. For patients who have been previously sensitized to BCG, the concentration can be reduced, typically to 10^4 – 10^5 CFU/ml and titrated to avoid inflammation at the injection site [1].

IL-2

Intratumoral administration of IL-2 is an effective local therapy for cutaneous melanoma, with response rates exceeding 80% with repeated administration of the drug, especially in smaller metastases [50,51]. However, there are no objective responses in concomitant distant metastases.

Table 2. Results of the most important series on hyperthermic isolated limb perfusion therapy with melphalan with or without TNF- α in advanced subcutaneous local recurrences or in-transit melanoma metastases in the extremities.

Study	Year(s)	Temperature (°C)	Patients (n)	Complete remission rate (%)	Partial remission rate (%)	Overall response rate (%)
Melphalan only						
Klaase	1978–1990	37–40	120	64	25	89
Kroon	1978–1986	37–38	43	77	2	79
Di Filippo	1969–1985	41.5	69	39	43	82
Lejeune	1977–1982	39–41	23	65	20	91
Skene	1979–1987	39–40	67	–	–	74
Rossi	1989–1996	40.5–41.5	49	51	30	81
Lejeune	1995	39–40	103	52	25	77
Lingan	1996	39–40	103	76	23	99
Thompson	1997	40–41	111	73	13	86
Bryant	1997	40–41	85	40	42	82
Di Filippo	1998	41.5–43	128	46	40	86
Melphalan plus TNF-α						
Lienard	1992	39–40	29	90	–	100
Fraker	1996	39–40	52	69	–	91
Lienard	1999	39–40	64	73	22	95
Eggermont	1995	39–40	58	88	12	100
Grunhagen	2005	39–40	100	69	26	95
Noorda	2004	39–40	90	59	–	–
Lejeune	1993	39–40	44	90	10	100

Adapted from [24].

Talimogene laherparepvec

A novel approach with systemic activity involves using oncolytic immunotherapy (talimogene laherparepvec [T-VEC]) derived from herpes simplex virus type-1, which is designed to replicate within tumors and to produce GM-CSF. Preliminary data from a trial comparing T-VEC repeatedly administered intra-tumorally with GM-CSF given subcutaneously in 436 patients with unresectable stage IIIB/C or IV melanoma with injectable subcutaneous tumors with or without limited visceral metastases were presented during the 2013 Annual Conference of American Society of Clinical Oncology (ASCO) [52]. The data showed objective responses in the T-VEC arm in 26% of patients as compared with 6% in the GM-CSF arm. Durable responses were strongly evident in stage IIIB/C disease (33%). Interim overall survival analysis showed a trend in favor of T-VEC. Further investigation in order to establish the appropriate use of this therapy in SM management is necessary.

Systemic immunotherapy & targeted therapy

Recent advances in the systemic therapy of metastatic melanoma, including immunotherapy (anti-CTLA4 and anti-PD-1) and targeted therapy (with BRAF/MEK inhibitors) has also had a significant impact on treatment modalities in SM (Table 3). These new therapies have significantly improved the progression-free and overall survival of advanced melanoma patients, and targeted therapy in particular is characterized by high response rates, while immunotherapy with

ipilimumab is related to long-term responses, mainly with low-burden and low-symptomatic disease. Therefore, in patients with indolent SMs with or without other distant metastases with minimal symptoms and of good performance status [53], upfront ipilimumab therapy should be considered, taking into account response kinetics (the responses need 2–4 months to occur, but if they do occur, they are long-lasting, with a median duration of response >19 months, possibly even leading to a cure of the disease in a small percentage of patients) and also potential serious adverse events related to autoimmunity. In cases with fast progressive and symptomatic disease in the presence of *BRAF* mutations, the treatment of choice is therapy with BRAF inhibitors (Figure 3), because these inhibitors are characterized by an induction of fast responses, although median time to progression related to secondary resistance is approximately 6 months. Vemurafenib and dabrafenib are potent inhibitors of mutated BRAF kinases that were shown to improve progression-free and overall survival in patients with stage IIIC or IV melanoma who tested positive for the *BRAF* V600E mutation [54,55]. Currently, there have been no studies evaluating these drugs specifically in locoregionally advanced melanoma.

The other option independent of *BRAF* status is the inclusion of patients into clinical trials (e.g., with drugs against PD-1). The acting on immune system checkpoints PD-1/PD-L1 (in monotherapy or in combination with anti-CTLA-4 antibodies) gives very promising results, with relatively high and durable objective tumor responses, as well as with limited,

Figure 3. The response of *BRAF*-mutated melanomas with subcutaneous metastases to vemurafenib after 2 months of therapy. (A) Pretreatment; (B) after 8 weeks of therapy.

Table 3. Novel registered agents and agents investigated in clinical trials for the treatment of advanced melanoma.

Name of drug	Approval/clinical trial status	Major activity data	Remarks/recommendations
Ipilimumab (anti-CTLA-4)	Approved for second-line therapy in Europe and for first-line therapy in the USA	Median OS: 10.1 (in pretreated patients) and 11.2 months (first-line); ORR: 11% (pretreated patients) and 15% (first-line); 2-year OS: 24% (second-line) and 28.5% (first-line); 4-year survival rate (Phase II data): >20%	Grade 3/4 toxicity in 15–56%, mainly autoimmunological AEs; responses are slow, but with long-term activity (or cure) in a limited population (approximately 20%); active in stable, asymptomatic brain metastases
Vemurafenib (BRAF inhibitor)	Approved in <i>BRAF</i> -mutated melanomas in both Europe and the USA	Median OS: 15 months; median PFS: 5.3–6.9 months; ORR: 48%; median time to response: 1.4 months	AEs typically comprise arthralgia, rash, fatigue, photosensitivity and development of keratoacanthoma or squamous cell carcinoma; responses are time-limited because almost all patients ultimately progress (with median PFS ~7 months)
Dabrafenib (BRAF inhibitor)	Approved in <i>BRAF</i> -mutated melanomas in both Europe and the USA	Median OS: 18.2 months; median PFS: 5.1–6.9 months	AEs typically comprise skin-related toxicities, fever, arthralgia and fatigue; fast responses but time-limited; activity also seen in untreated brain metastases
Trametinib (MEK inhibitor)	Approved in <i>BRAF</i> -mutated melanomas in the USA only	Median PFS: 4.8 months; 6-month OS rate: 81%	Common AEs: rash, diarrhea and peripheral edema; weaker activity than BRAF inhibitor monotherapy, currently tested in combination with dabrafenib
Nivolumab (anti-PD-1)	Phase III trial, ongoing	ORR at optimal dose: 41%; 12-month PFS: 36%; 1-year OS: 62% (82% in combination with ipilimumab)	Grade 3/4 toxicity in 14%; faster responses than after anti-CTLA-4 treatment; correlation of activity with PD-L1 expression in tumor tissue
MK-3475 (anti-PD-1)	Phase III trial, ongoing	ORR at optimal dose: 52%; median PFS: >7 months	Grade 3/4 toxicity in 13%; faster responses than after anti-CTLA-4 treatment; demonstrates activity in patients pretreated with ipilimumab

AE: Adverse event; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.

manageable toxicity [54]. The Phase III trials of the anti-PD-1 strategy are ongoing, comprising patients with unresectable stage IIIC or IVA tumors.

It should be noted that many specialists are trying to reserve systemic therapy for distant metastases beyond the extremities or after failure of all locoregional treatment options.

Conclusion

Taking into account the number of different treatment options in SM of cutaneous melanoma, therapy should be individualized after discussion with a multidisciplinary expert team. Although a subset of patients can be cured, therapy is challenging because of the different extents, locations and distributions of lesions, as well as their biological behaviors. There are some proposed of decision trees [4] combining treatment guidelines and ‘individualized approaches’, but they are not based on randomized trials comparing the different approaches to SM/IT melanomas. Nonetheless, local therapy is preferred in limited disease, locoregional therapy (HILP or ILI) is preferred

in extensive or recurrent lesions in extremity locations and ECT can be the palliative option in different locations when a fast, less morbid technique than HILP is required for the management of bleeding or painful lesions. However, in case of progressive disease the new systemic therapies, including immunotherapy and targeted therapy, should be utilized giving the chance for further durable responses.

Future perspective

The near future of SM therapy will be based on a combination of different local, locoregional and systemic modalities. The local recurrences or partial remissions after HILP/ILI can be effectively treated with ECT. On the other hand, local modalities can be also combined with new systemic modalities if CR is not achieved. We can soon expect a major improvement in the long-term outcomes of patients with SM.

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