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Chemotherapy

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1. Introduction

The number of melanoma cases worldwide is increasing faster than any other cancer. Although early detection, appropriate surgery, and adjuvant therapy have improved outcomes, the prognosis of metastatic melanoma remains very poor. Advanced melanoma is still associated with an extremely poor median survival, ranging from 2 to 8 months, with only 5% surviving more than 5 years and remains one of the most treatment-refractory malignancies. Many agents have been investigated for antitumor activity in melanoma but the current treatment options for patients with metastatic disease are limited and non-curative in the majority of cases (Mouawad et al, 2010).

The treatment of a patient with metastatic melanoma depends on multiple factors including the overall condition and age of the patient, the sites and number of metastases, pace of the disease, and the patient's wishes for treatment. Currently, the goals of treatment are directed toward palliation of symptoms, particularly if the improvement in the symptoms related to the disease exceeds the side effects associated with the therapy (Green & Schuchter, 1998).

In advanced melanoma, single agent chemotherapy, combination chemotherapy, biochemotherapy (chemoimmunotherapy), targeted therapy, Toll-like receptor agonists and antiangiogenic therapies have been used (Bhatia et al., 2009; Chowdhury, 1999; Cohen & Falkson, 1998; Jilaveanu et al., 2009; Lutzky, 2010; O'Day et al, 2002; Tarhini & Agarwala, 2006; Treisman & Garlie, 2010).

In this chapter, classical chemotherapeutic agents, regimens and new chemotherapeutics, such as targeted therapies for melanoma treatment have been reviewed.

2. Chemotherapy

Melanoma is considered a chemotherapy-resistant disease, and systemic chemotherapy has failed to significantly improve the survival of patients with nonresectable metastatic melanoma. The disease frequently becomes refractory to the agents even after initial responses are observed. Despite the lack of curative effect for the patient with advanced metastatic disease, chemotherapy continues to play a role in palliation of the disease. Although many agents have been used for melanoma treatment, single agent chemotherapy has generally been considered ineffective. Despite the poor overall outcome with these agents, they are still in common use in the clinic (Treisman & Garlie, 2010).

For stage IV melanoma, palliative systemic chemotherapy is the mainstay of treatment and is associated with median survival durations with combination regimens of 6-9 months and

5-year survival rates of approximately 6%, which are not influenced significantly by any therapy yet tested in rigorous multicentre cooperative group trials (Eggermont & Kirkwood, 2004).

2.1 Single agent chemotherapy

A large number of clinical trials have tested different single drugs like alkylating agents, nitrosureas, vinca alkaloids, platinum drugs, taxanes, topoisomerase inhibitors and anthracyclines, but few have shown an objective response rate (<20%) or an increase in progression-free and overall survival rates (Mouawad et al, 2010).

2.1.1 Alkylating agents

Dacarbazine (DTIC) is the first US Food and Drug Administration (FDA) approved chemotherapeutic agent for the treatment of metastatic melanoma (Green & Schuchter, 1998; Mouawad et al, 2010). The response rates with dacarbazine were 15-25%, with median response durations of 5-6 months, but less than 5% of complete responses. Long-term follow-up of patients treated with DTIC alone shows that less than 2% of the patients could survive for 6 years (Mouawad et al, 2010, Sasse et al., 2009). DTIC is a prodrug of the alkylating agent 5-(3-methyltriazen-1-yl) imidazole-4-carboximide (MTIC). The drug is generally well tolerated, with nausea as its major side effect, which can be controlled with antiemetic therapy (Treisman & Garlie, 2010). Doses and schedules of DTIC vary widely, with no data suggest that response rates are influenced by these variables. The most commonly used regimen is 850-1000 mg/m^2 intravenously, on day 1 only, repeated every 3 weeks (Green & Schuchter, 1998). It can be applied 200 mg/m^2 intravenously daily for 5 days every 3 weeks (Jilaveanu et al., 2009). It is more effective for subcutaneous, lymph node, and pulmonary metastases (Jilaveanu et al., 2009), but it is ineffective in brain metastases (Marsden et al., 2010). DTIC has been used as a standard for comparing the efficacy of new regimens (Coit et al., 2011; Marsden et al., 2010).

Temozolomide (TMZ), an imidazotetrazine derivative of dacarbazine, is another cytotoxic alkylating agent and has the same active metabolite as dacarbazine. It is usually used to treat solid tumors, such as brain tumors, due to its ability to cross the blood-brain barrier, and might therefore constitute an alternative to DTIC in treating brain metastases, for which dacarbazine is ineffective (Jilaveanu et al., 2009; Treisman & Garlie, 2010).

TMZ was shown to have an objective response rate of 21% (12 of 56 patients) in a phase II study, with a median survival time of 5.5 months (Treisman & Garlie, 2010). Temolozomide was equivalent to dacarbazine in treating metastatic melanoma in a large randomized trial of melanoma patients with incipient metastatic disease. It was administered orally to one group at a dose of 200 mg/m^2 for 5 days every 4 weeks and compared with dacarbazine administered iv at 250 mg/m^2 for 5 days every 3 weeks. The median overall survival was 7.7 months for patients treated with TMZ and 6.4 for those treated with DTIC. The 6-month overall survival rate was 61% and 51%, respectively; the overall survival was not statistically significant. The median progression-free survival was significantly longer in patients treated with temozolomide (1.9 months versus 1.5 months). No big differences were observed in toxicity between the two drugs (Jilaveanu et al., 2009). The results of another multicentre phase III trial that randomized 859 patients to receive DTIC vs an extended dosing schedule of TMZ (150 mg/m^2/d on 7 consecutive days every 14 days) were recently reported. The investigators found no significant differences between DTIC and TMZ in objective response rate, progression-free survival, or overall survival (Bhatia et al., 2009).

Although temozolomide administered as a single agent might have some advantages in a select group of patients, it has not been FDA-approved for advanced stage melanoma; however, it is widely used in the United States. Temozolomide and dacarbazine are being studied in combination with other therapies (Jilaveanu et al., 2009). The addition of IFN to TMZ resulted in higher response rates; however, survival was similar for both treatments and the combination was associated with higher toxicity. TMZ has shown promising results in the treatment of brain metastases from melanoma and may be a reasonable option if surgery or radiation is not appropriate (Quirt et al., 2007).
In a randomized phase III study, Middleton et al. compared dacarbazine and temozolomide in 305 patients with advanced melanoma. They found that median survival time was 7.7 months for patients treated with temozolomide and 6.4 months for those treated with DTIC. Median progression-free survival was significantly longer in the temozolomide-treated group (1.9 months) than in the DTIC-treated group (1.5 months) ($p=0.012$). No major difference in drug safety was observed. Temozolomide therapy improved health-related quality of life; more patients showed improvement or maintenance of physical functioning at week 12. They concluded that temozolomide demonstrated efficacy equal to that of DTIC and was an oral alternative for patients with advanced metastatic melanoma (Middleton et al., 2000).

2.1.2 Antimicrotubular agents

Microtubular toxins and microtubular disassembly inhibitors have both been used in patients with metastatic melanoma. The vinca alkaloids especially vinblastine and vindesine, based on their modest activities and limited toxicities, have primarily been used in combination therapy (Mouawad et al., 2010; Treisman & Garlie, 2010). They are not effective as monotherapy. Vinflunine ditartrate and vinorelbine are the other vinca alkaloid agents that have been used in phase II trials (Jilaveanu et al., 2009).
Paclitaxel and docetaxel, taxanes, are microtubule disassembly inhibitors with antitumor activity in a variety of neoplastic diseases. Paclitaxel has been evaluated in several phase I and II studies, and has demonstrated an approximately 12% to 16% response rate in previously untreated patients. Paclitaxel is commonly used in combination with carboplatin in other malignancies, and was similarly tested in melanoma (Treisman & Garlie, 2010). Weekly administration of paclitaxel at a dose of 80 to 100 mg/m^2 (on days 1, 8, and 15 every 4 weeks) is well tolerated by most patients. Alternatively, a higher dose can be administered once every 3 to 4 weeks (Bhatia et al., 2009). A phase II docetaxel study showed a 12.5% response rate in melanoma with one of the patients having a durable complete response, and it still being actively studied in other combinations, with some benefit (Treisman & Garlie, 2010). Several studies have evaluated docetaxel, at a dose of 100 mg/m^2 administered intravenously over 1 hour every 21 days, with response rates ranging from 15% to 19% (Green & Schuchter, 1998).
Associated toxicities include fatique, alopecia, myelosuppression, neuropathy, myalgias, and hypersensitivity reactions (Bhatia et al., 2009).

2.1.3 Platinum analogs

Cisplatin and carboplatin have modest activity in patients with metastatic melanoma. Single agent cisplatin given at conventional doses yields a response rate of less than 10%. However, a phase II study that used a higher dose (150 mg/m^2) of cisplatin in combination with

amifostine reported an objective response rate of 53%, although the responses were shortlived. A response rate of 19% was observed with carboplatin in a phase II study in chemotherapy-naive patients with metastatic melanoma. Carboplatin has also been used in combination with paclitaxel in previously treated patients (Bhatia et al., 2009).

2.1.4 Nitrosoureas

The nitrosoureas are a group of alkylating agents that act by cross-linking DNA (Treisman & Garlie, 2010). Carmustine (BCNU), lomustine (CCNU) and fotemustine have single-agent activity comparable to dacarbazine, although they cause more myelosuppression and alopecia. A chloroethyl nitrosourea, fotemustine rapidly crosses the blood-brain barrier and has been found to have encouraging activity in patients with brain metastases. When compared to dacarbazine in a phase III trial involving 229 patients with metastatic melanoma, fotemustine was associated with a higher objective response rate (15% vs 7%, respectively) and a trend toward improved survival (7.3 vs 5.6 months, respectively). In patients without brain metastases at inclusion, the median time to development of brain metastases was 22.7 months in the fotemustine arm vs 7.2 months in the dacarbazine arm. Fotemustine has not been approved by the FDA but is available in Europe (Bhatia et al., 2009).

In clinical practice, these agents have a limited role as single agents, but have been used in combination chemotherapy (Treisman & Garlie, 2010).

2.1.5 Tamoxifen

The identification of estrogen receptors in melanoma led to initial trials of hormonal therapy for the diseases, and tamoxifen, an estrogen receptor antagonist, might be considered one of the first targeted agents used for the therapy for melanoma. Tamoxifen was initially used as a single agent and then in combination with various chemotherapeutic regimens. Although initial studies suggested a benefit for tamoxifen as a single agent in the treatment of metastatic melanoma, subsequent studies showed a response rate of only 5%. In addition, evaluation of samples using immunostaining failed to demonstrate estrogen receptors. Tamoxifen could have several other effects including effects on angiogenesis, synergic effects with chemotherapy, and reversal of multidrug resistance. More recently, preclinical studies have shown that tamoxifen potentiates the cytotoxic action of chemotherapeutic agents, specifically DTIC and cisplatin (Green & Schuchter, 1998). Several randomized clinical trials have been conducted to assess the therapeutic benefit of tamoxifen in combination chemotherapy regimens. Cocconi et al of the Group of Italian Investigators For Cancer Research (GOIRC) compared DTIC alone to DTIC plus tamoxifen in a study of 117 patients. They found a statistically significant survival advantage to tamoxifen (48 weeks versus 29 weeks) and a higher response rate in patients receiving DTIC and tamoxifen compared with DTIC alone (Cocconi & Bella et al., 1992). In another randomized clinical trial, Rusthoven et al of the National Cancer Institute of Canada (NCIC) conducted a double-blind, placebo-controlled trial comparing response rates and survival of 200 patients receiving the Dartmouth regimen with and without tamoxifen. There was no statistically significant difference between the two groups in either overall response rate or survival (Rusthoven & Quirt et al., 1996).

In a metaanalysis of published randomized controlled trials involved 912 patients, it has been demonstrated that tamoxifen does not improve the overall response rate, complete

response rate, or survival rate when administered along with combined chemotherapy or biochemotherapy regimens (Lens et al., 2003).
Single drugs used in metastatic melanoma have been summarized in table 1.

Drugs	Abbreviation	Number of patients	Dose	Overall response	References
Dacarbazine	DTIC	1868	250 mg/m²/day x 5 d	15-25%	Hill 2nd et al., 1979
Temozolomide	TMZ	305	150-200 mg/m²/day x 5 d	14%	Bleehen et al., 1995; Newlands et al., 1992
Carmustine	BCNU	122	75-110 mg/m²	13-18%	Ahmann et al., 1976
Semustine	MET-CCNU	347	130 mg/m²	16%	Ahmann et al., 1976
Fotemustine	FTMU	153	100 mg/m²/week x 3 w	20-25%	Jacquillat et al., 1990
Cisplatin	CDDP	114	60-150 mg/m²	15%	Glover et al., 1987
Carboplatin	CBDCA	30	400 mg/m² iv every 4 weeks	19%	Evans et al., 1987
Vindezine	VDS	273	3 mg/m² slow iv (7-14 day intervals)	14%	Quagliana et al., 1984
Vinblastine	VLB	62	6-8 mg/m² slow iv 1/week	13%	Quagliana et al., 1984
Docetaxel	TXT	43	100 mg/m² iv every 21 days	14%	Aamdal et al., 1994
Paclitaxel	TXL	34	125-275 mg/m²	15%	Einzig AI et al., 1991
Tamoxifen	TAM	172	20 mg/day orally	7%	Rumke et al., 1992

Table 1. Single drugs used in metastatic melanoma

2.2 Combination chemotherapy

The role of combination chemotherapy in the treatment of metastatic melanoma remains uncertain. Historically there have been suggestions of improved activity with combination regimens, but reports of high response rates have generally emerged from single institution studies, and when large multicentre trials have been performed they have not confirmed these improvements (Chowdhury et al., 1999). There are a numerous combinations of chemotherapy for melanoma that have been are being developed and studied. These regimens have generally employed DTIC or, more recently, TMZ. Larger multiinstitution studies and results of randomized clinical trials strongly suggest that DTIC alone is as good as any of the combination regimens. Various combinations of DTIC, nitrosoureas, and cisplatin with other chemotherapeutic agents have been extensively evaluated in phase II

clinical trials, with response rates ranging from 20% to 40%. The more commonly tested combinations are presented in table 2.

A four-drug combination referred to as the BOLD regimen which includes bleomycin, vincristine, CCNU and DTIC was first studied regimen. Initial studies produced a response rate of 40%, with a 9% complete response rate. Follow-up phase II studies failed to confirm these results, with subsequent response rates falling to 4% to 20%. Another chemotherapeutic regimen extensively evaluated is the combination of vinblastine, cisplatin, and DTIC (CVD regimen), which was developed by Legha and colleagues. The response rates with this three-drug regimen range from 24% to 45% (Green & Schuchter, 1998). The Dartmouth regimen (CDBT) (McClay regimen) is a combination of cisplatin, carmustine, DTIC, and tamoxifen (NCCN Guidelines Version 2011 Melanoma, Treisman & Garlie, 2010).

Regimen	Doses	Response rate
BOLD	Bleomycin, 15 U day 1,4 Vincristine, 1mg/m^2 day 1,4 CCNU, 80 mg/m^2 day 1 DTIC, 200 mg/m^2 day 1-5 28-day cycles	9%-40%
CVD	Cisplatin, 20 mg/m^2 day 2-5 Vinblastine, 1.6 mg/m^2 day 1-5 DTIC, 800 mg/m^2 day 1 21-day cycles	24%-45%
CBDT (Dartmouth)	Cisplatin, 25 mg/m^2 day 1-3 BCNU, 150 mg/m^2 day 1 (given every other cycle) DTIC, 220 mg/m^2 day 1-3 Tamoxifen, 20 mg/day 21-day cycles	19%-55%

Table 2. Combination chemotherapy regimens in metastatic melanoma

In a large phase III study comparing the CVD regimen to DTIC alone, there was a trend toward improved response and survival. The Dartmouth regimen originally resulted in a 55% response rate in the initial series of 20 patients with metastatic melanoma (Treisman & Garlie, 2010). A phase III multicentre trial that randomized 240 patients to the Dartmouth regimen vs dacarbazine monotherapy did not show a statistically significant benefit in favor of the combination. Despite a modest difference in objective response rate in favor of CDBT over DTIC (16.8% and 9.9%, respectively; p=.13), there was no significant difference in overall survival (7.7 and 6.3 months, respectively; p=.52). Myelosuppression, fatique, nausea, and vomiting were significantly higher in the CDBT arm (Chapman et al., 1999).

Sileni et al. compared the activity and toxicity of the combination of dacarbazine, carmustine, cisplatin and tamoxifen (DBDT regimen) versus DTIC alone in patients with metastatic melanoma. Sixty patients were randomly assigned to receive BCNU 150 mg/m^2 intravenously on day 1, cisplatin 25 mg/m^2 iv. daily on days 1 to 3, DTIC 220 mg/m^2 iv

daily on days 1 to 3 and tamoxifen 160 mg orally daily for 7 days prior to chemotherapy (DBDT arm). Treatment cycles were repeated every 28 days, while BCNU was given every two cycles. The DTIC arm patients received DTIC alone 1200 mg/m^2 iv on day 1, repeated every 21 days. The overall response rate was 26% in the DBDT arm and 5% in the DTIC arm. Complete responses were 2.5% for DBDT and 0% for DTIC. The median progression-free survival and median survival were 4 and 9 months, respectively for DBDT, and 2 and 7 months for DTIC. DBDT was associated with significant haematological toxicity: 33% of the patients experienced a grade III or IV neutropenia and 28% a grade III or IV thrombocytopenia. The overall response rate obtained with DBDT was greater than that obtained with DTIC alone; however, this combination increased toxicity (Sileni et al., 2001).

The combination of paclitaxel and carboplatin (PC) has been reported to have antitumor activity in patients with metastatic melanoma, including patients who have received prior chemotherapy (Bhatia et al., 2009).

Zimpfer-Rechner et al. performed a randomized, multicentre, second-line clinical phase II study of paclitaxel either as monotherapy or combined with carboplatin given on an outpatient basis. In arm A, paclitaxel was administered at a dose of 100 mg/m^2 intravenously on day 1 each week for 6 weeks. In arm B, paclitaxel was administered at a dose of 80 mg/m^2 intravenously followed by carboplatin 200 mg/m^2 on day 1 each week for 6 weeks. The next cycle was administered after a 2 week intermission. The study was stopped after 40 patients because the overall response rate was below 10% in both arms. The median survival time after initiation of second-line treatment was 209 days for patients treated with paclitaxel only, and 218 days for those treated with paclitaxel/carboplatin. The median time to progression was around 56 days in both arms. Paclitaxel with or without carboplatin had only limited efficacy, and the combination of these drugs adds significantly to haematological toxicity without improving response or survival rates (Zimpfer-Rechner et al., 2003).

Rao et al. published their results with the combination of paclitaxel and carboplatin in 31 patients with metastatic melanoma. These patients had a median of two previous therapies, with the majority (29; 94%) having failed prior temozolomide or dacarbazine therapy. The most commonly used regimen was weekly paclitaxel (at a dose of 100 mg/m^2) and carboplatin administered on days 1,8, and 15 of a 28-day cycle. An objective partial response was noted in 8 patients (26%) with an additional 6 patients (19%) having stable disease; a clinical benefit was noted in 45% of those patients treated. The median time to disease progression was 3 months (range, 0-7 mos), with a median overall survival of 7.8 months (range, 1-14 mos). They concluded that the combination of paclitaxel and carboplatin appeared to have definite and clinically meaningful activity when used as second-line therapy after temozolomide or dacarbazine (Rao et al., 2006).

In a report on synthesis of randomized trials, 48 studies having 111 active treatment arms (24 with dacarbazine monotherapy, n=1390; 75 with dacarbazine combinations, n=4962; 12 with non-dacarbazine treatments, n=783) treating 7135 patients were examined. Response to dacarbazine monotherapy ranged between 5.3% and 28% (average 15.3%). Partial responses comprised 73% of successes. Only adding interferons improved response rates but survival duration was not significantly longer. All other treatments alone or in combination were ineffective (Lui et al., 2007).

A listing of major randomized studies evaluating DTIC versus drug combination is summarized in table 3.

Control arm dacarbazine dose/schedule	Study arm drugs (dose/schedule)	No. of randomised patients	Overall response (%)	Overall survival (months)	Study by
2 mg/kg/day (iv) × 10 days	Carmustine 150 mg/m² (iv) + vincristine 2 mg/m² (iv) on day 1 only	50	22 vs 25	NA	Bellet et al., 1976
250 mg/m² (iv) on days 1–5 every 3 weeks	Cisplatin 20 mg/m²/day for 4 days starting on day 2 + vinblastine 1.6 mg/m²/day × 5 days + dacarbazine 800 mg/m² (iv) on day 1	104	11 vs 24	5 vs 6	Buzaid et al., 1993
1000 mg/m² bid short iv infusion every 3 weeks	Tamoxifen 10 mg twice daily by mouth 1 week before chemotherapy +carmustine 150 mg/m² on day 1+dacarbazine 220 mg/m² (iv)+cicplatin 25 mg/m²/days 1-3	240	10.2 vs 18.5	6.3 vs 7.7	Chapman et al., 1999
250 mg/m² (iv) for 4 days every 3 weeks	Dacarbazine 250 mg/m² (iv) days 1–4 every 3 weeks + detorubicin 120 mg/m² iv every 3 weeks	51	15 vs 36	5 vs 6	Chauvergne et al., 1982
1200 mg/m² day 1 every 3 weeks	Carmustine 150 mg/m² (iv) on day 1 + cisplatin 25 mg/m² (iv)/day on days 1–3 + dacarbazine 220 mg/m² (iv)/day on days 1–3 + tamoxifen 160 mg orally/day × 7 days prior to chemotherapy. Treatment cycles repeated every 28 days, BCNU every 2 cycles	60	6 vs 26	7 vs 9	Chiarion Sileni et al., 2001
2.5 mg/m² (I.V.) injection on days 1–4 every 4 weeks	Dacarbazine 2.5 mg/m² (iv) by means of bolus injection on days 1–4 every 4 weeks + corynebacterium parvum 7 mg (im) 1 week before starting DTIC and at 4-week intervals thereafter	49	22 vs 27	5 vs 5	Clunie et al., 1980
250 mg/m² on days 1–5 every 3 weeks	Dacarbazine 250 mg/m² (iv) × 5 days, every 3-weeks + tamoxifen 20 mg/m² orally daily	117	12 vs 28	11.8 vs 7.25	Cocconi et al., 1992

Control arm dacarbazine dose/schedule	Study arm drugs (dose/schedule)	No. of randomised patients	Overall response (%)	Overall survival (months)	Study by
200 mg/m² (iv) for 5 days repeated every 3 weeks	po methyl-CCNU 200 mg/m² once every 6 weeks Dacarbazine 150 mg/m² (iv) × 5 days/3 weeks + po methyl-CCNU 130 mg/m²1/6 weeks	415	15 vs 15 15 vs 14	4.0 vs 4.2 4.0 vs 4.0	Costanza et al., 1977
250 mg/m² (iv) on days 1–5 every 3 weeks	Dacarbazine 250 mg/m² (iv)/day on days 1–5 + epirubicin 90 mg/m² on day 1 every 3 weeks	42	9 vs 21	NA	Lopez et al., 1984
250 mg/m² (iv) on days 1–10 every 4 weeks	Vinblastine 6 mg/m²/day (iv) on days 1–2 + 24-h infusion of bleomycin 15 units/m² from days 1–5 + cisplatin 50 mg/m² 1 h (iv) infusion on day 5. After four courses, vinblastine and cisplatin were given alone. Courses repeated on a cycle of 4 weeks	77	14 vs 10	4.1 vs 3.42	Luikart et al., 1984
300 mg/m²/day × 6 days every month days.	Dacarbazine 100 mg/m²/8 h × 6 days every month days Carmustine 150 mg/m² + vincristine 2 mg/m² every 30 days	120	32 vs 29 32 vs 24	8.5 vs 8.4 8.5 vs 6.5	Moon et al., 1975
250 mg/m²/day (iv) for 5 days every 4 weeks	Dacarbazine 250 mg/m²/day (iv) × 5 days every 4 weeks + vindesine 3 mg/m²/week	119	18 vs 25	4.1 vs 5.7	Ringborg et al., 1989
220 mg/m² on days 1–3, q 21 days	Dacarbazine 220 mg/m² on day 1–3 + carboplatine AUC 5, day 1, q 21 days	148	11.7 vs 21.3	7 vs 9	Babovic et al., 2008
200 mg/m²/day (iv) for 5 days every 28 days	Arm 2: (I.V.) IFN-α 15 MU/m²/day days 1–5 × 3 weeks, then (sc) 10 MU/m² 3×/week + dacarbazine 200 mg/m² daily (iv) days 1–5 starting on day 22, every 28 days Arm 3: orally tamoxifen 20 mg/day starting day 1 + dacarbazine 200 mg/m²/day	280	15 vs 21 15 vs 18 15 vs 19	9.99 vs 9.33 9.99 vs 7.97 9.99 vs 9.54	Falkson et al., 1998

Control arm dacarbazine dose/schedule	Study arm drugs (dose/schedule)	No. of randomised patients	Overall response (%)	Overall survival (months)	Study by
	(iv) days 1–5 every 28 days Arm 4: (iv) IFN-α 15 MU/m²/day days 1–5 × 3 weeks, then (sc) 10 MU/m² 3×/week + orally tamoxifen 20 mg/day starting day 1 + dacarbazine 200 mg/m²/day (iv) days 1–5/28 days				
800 mg/m² (iv) on days 1 and 21	Dacarbazine 800 mg/m² (iv) days 1 and 21 + daily (im) INF-α 3 MIU at days 1–3, 6 MlU days 4–6, and 9 MIU daily thereafter. Started concomitantly Dacarbazine 800 mg/m² (iv) days 1 and 21 + (IM) INF-α 3 MIU 3×/week. Started concomitantly	266	20 vs 28 20 vs 23	11 vs 13 11 vs 11	Bajetta et al., 1994
800 mg/m² (iv) every 3 weeks	Dacarbazine (iv) escalating dose 200 mg/m², 400 mg/m², 800 mg/m²/3 weeks; sc IFN-α starting at 3 MU/day on days 1–3, 9 MU/day on days 4–70, then 9 MU 3×/week	170	17 vs 21	7.36 vs 6.27	Thomson et al., 1993

Table 3. Key randomized studies evaluating dacarbazine (DTIC) vs drug combination

2.3 Biochemotherapy

Biochemotherapy, the combination of chemotherapy and biologic response modifiers, was developed in the early 1990s to improve response rates and durable remissions in metastatic melanoma. The initial regimens were given sequentially (chemotherapy followed by biologic response modifiers) because of concern of toxicity if all the drugs were given simultaneously. Paradoxically, sequential regimens were highly toxic because of the duration of treatment (10 to 14 days) and the combined and non-overlapping toxicities of chemotherapy and biologic response modifiers (O'day et al., 2002). An outpatient biochemotherapy regimen (carmustine, cisplatin, dacarbazine, tamoxifen, IL-2 and interferon with lower dose subcutaneous IL-2 and interferon) was developed by Thompson et al (Thompson et al., 1997). The first concurrent inpatient biochemotherapy regimen was developed by Legha et al. „Legha regimen" combined cisplatin, vinblastine and dacarbazine (CVD) chemotherapy with continuous infusion IL-2 (9 MU/m² per day) for 4 days and 5

days of subcutaneous interferon alfa (5 MU/m² per day) at 21-day intervals. The results were encouraging with an overall response rate of 64%, a complete response rate of 21%, median survival of 12 months, and a 2-year survival rate of 10%. Efficacy was comparable to the inpatient sequential regimens, but the regimen was significantly less toxic. Fever/neutropenia occured in 64% of patients and was the most significant reversible toxicity (Legha et al., 1998; O'day et al., 2002). The Legha regimen was subsequently modified by McDermott et al. to reduce toxicity. The modifications included reduction in the vinblastine dose, empiric granulocyte colony-stimulating factor (G-CSF) posttreatment, routine 5-HT3 antagonist anti-emetic therapy, prophylactic antibiotics, frequent changes in central lines, dose reductions for toxicity, and limitation of treatment to a maximum of 4 cycles of therapy (McDermott et al., 2000). In a phase II trial with these modifications, toxicity was improved and the response rate was 48%, the complete remission rate was 20%, and the median survival was 11 months. Fever/neutropenia was not observed. G-CSF has now become a standard component of concurrent biochemotherapy regimens. Further modifications of the Legha regimen have been published with decrescendo dosing of continuous infusion IL-2. The rationale for decrescendo dosing of IL-2 is based on improved clinical response and reduced cumulative IL-2 toxicity (O'day et al., 2002).

Ridolfi et al conducted a multicenter prospective randomized clinical trial in outpatients with metastatic melanoma to compare chemotherapy with biochemotherapy using immunomodulant doses of IL-2 and IFNα-2b. They randomized 176 patients with advanced melanoma to receive chemotherapy (cisplatin and dacarbazine with or without carmustine every 21 days) or biochemotherapy comprising the same chemotherapy regimen followed by low-dose subcutaneous IL-2 for 8 days and IFNα-2b three times a week, both for six cycles. At a median follow-up of 18 (chemotherapy) and 16 (biochemotherapy) months, median overall survival was 9.5 versus 11.0 months (p=.51), respectively. Treatment-related toxicity was fairly similar in both groups. They concluded that the addition of low-dose immunotherapy did not produce a significant advantage in overall survival, time to progression, or overall response (Ridolfi et al., 2002).

Bajetta et al. investigated the effects of additional cytokines to chemotherapy in 151 untreated metastatic melanoma patients. 75 patients received cisplatin 30 mg/m² on days 1-3, vindesine 2.5 mg/m² on day 1 and dacarbazine 250 mg/m² on days 1-3. 76 patients received same CVD scheme plus interferon-α2b on days 1-5 and interleukin-2 on days 1-5 and 8-15, both administered subcutaneously, either recycled every 3 weeks. 10% of the patients were alive at a median of 52 months from start of therapy. They observed a response rate of 21% on arm A versus 33% on arm B; three patients (4%) given biochemotherapy had complete responses. Median time to progression was identical; median overall survival time was 12 months on arm A and 11 months on arm B. They also concluded that biochemotherapy was not better than chemotherapy alone, therefore biochemotherapy can not be recommended as standard first-line therapy for metastatic melanoma (Bajetta et al., 2006).

3. Novel targeted agents

The mitogen-activated protein kinase pathway plays a key role in melanoma development and is an important therapeutic target. Disregulation of this pathway may result in increased signalling activity leading to proliferation, invasion, metastasis, migration,

survival and angiogenesis. Activating mutations in the BRAF and NRAS genes have been found to be relatively frequent in melanoma, occurring in approximately 50-60% and 15% of tumors, respectively (Lutzky, 2010). It has been shown that mutations in the KIT gene are more frequent in patients with melanomas arising from mucosal, acral and sun-damaged skin primary sites. NRAS and BRAF mutated melanomas are more commonly derived from non sun-damaged skin (Curtin et al., 2005; Curtin et al., 2006).

Recent reports describing major responses in KIT-mutated melanomas treated with imatinib mesylate and other drugs that inhibit KIT tyrosine kinase have led to larger trials of imatinib mesylate in mutation enriched populations, in an attempt to confirm that mutated KIT is a clinically important target in this small subpopulation of patients with melanoma. The most common BRAF mutation in melanoma (in 90% of BRAF-mutated melanomas) is the V600E mutation, which activates BRAF 500-fold. Sorafenib inhibits the BRAF serine/threonine kinase as well as various receptor tyrosine kinases, with significant activity in the VEGFR. Two randomized clinical trials testing sorafenib in combination with chemotherapy in melanoma produced negative results. The most likely explanation is that sorafenib is not very active against V600E mutated BRAF kinase. More specific BRAF-targeting drugs have been developed are under investigation. In a phase I trial recently published, PLX4032, an oral, selective inhibitor of oncogenic V600E BRAF kinase, induced complete or partial tumor regression in 81% of patients who had melanoma with the V600E BRAF mutation, with responses being observed in all sites of disease. Cutaneous side effects, fatigue and arthralgia were the most common side effects (Lutzky, 2010).

In a phase II study evaluating the effects of sorafenib in advanced melanoma, a total of 101 patients received placebo plus dacarbazine (n=50) or sorafenib plus dacarbazine (n=51). On day 1 of a 21-day cycle, patients received intravenous dacarbazine 1000 mg/m^2 for a maximum of 16 cycles. Oral sorafenib 400 mg or placebo was administered twice a day continuously. Median progression-free survival in the sorafenib plus dacarbazine arm was 21.1 weeks versus 11.7 weeks in the placebo plus dacarbazine arm (p=0.068). There were statistically significant improvements in progression-free survival rates at 6 and 9 months, and in time to progression in favour of the sorafenib plus dacarbazine arm. No difference in overall survival was observed. Sorafenib plus dacarbazine was well tolerated in patients with advanced melanoma and yielded an encouraging improvement in progression-free survival (McDermott et al., 2008). Hauschild et al reported a phase III randomized, placebo-controlled study on the efficacy and safety of sorafenib with carboplatin and paclitaxel in advanced melanoma who had progressed on a dacarbazine-or temozolomide-containing regimen. A total of 270 patients were randomly assigned to receive intravenous paclitaxel 225 mg/m^2 plus intravenous carboplatin at area under curve 6 (AUC 6) on day 1 of a 21-day cycle followed by either placebo (n=135) or oral sorafenib 400 mg (n=135) twice daily on days 2 to 19. The median progression-free time was 17.9 weeks for the placebo plus carboplatin arm and 17.4 weeks for the sorafenib plus carboplatin arm (p=.49). Response rate was 11% with placebo versus 12% with sorafenib. Grade III thrombocytopenia, diarrhea, and fatigue were more common in patients treated with sorafenib plus carboplatin versus placebo plus carboplatin. The addition of sorafenib to carboplatin did not improve any of the end points over placebo plus carboplatin in this study (Hauschild et al., 2009).

BAY 43-9006 is a novel RAF inhibitor that inhibits B-RAF and C-RAF. It is orally available and has been shown to be well tolerated. In a phase I/II trial of BAY 43-9006 in combination with carboplatin and paclitaxel, 35 melanoma patients were treated for at least 6 weeks. Among 32 evaluable patients, 11 (34%) had partial responses, including 10 ongoing at 3-16 months. Nineteen patients had stable disease as best response. The combination demonstrated activity in melanoma and had a favourable safety profile and no apparent pharmacokinetic interactions (Tarhini & Agarwala, 2006).

Angiogenesis and signalling through the ref/mitogen-activated protein/extracellular signal-regulated kinase/extracellular signal-regulated kinase cascade have been reported to play important roles in melanoma. Ref/mitogen-activated protein/extracellular signal-regulated kinase inhibitor AZD6244 is a new targeted agent for advanced melanoma (Friday & Adjei, 2008). Other important molecular pathways have been found to be altered in melanoma, opening new avenues for therapeutic intervention. These include the phosphatidylinositol-3-kinase, microphtalmia-associated transcription factor, cyclin-dependent kinases, notch-1 and iNOS pathways. Early clinical trials with drugs that are active in these pathways are being conducted (Lutzky, 2010).

4. Conclusion

Metastatic melanoma has remained refractory to systemic treatment for decades. Single-agent or combination chemotherapy or biologic response modifiers alone have not resulted in response rates of durable remissions that are high enough to affect median survival. In the past decade, biochemotherapy regimens have been developed that appear to produce systemic response in approximately 50% patients and durable remissions in 10% to 20%. Modified concurrent biochemotherapy regimens have preserved efficacy and reduced toxicity, thus allowing for larger community-based clinical trials that are currently ongoing. These trials will determine the role of biochemotherapy as first-line treatment for metastatic disease. Further understanding of the molecular and immunologic mechanisms that promote survival of melanoma tumor cells will undoubtedly lead to the development of better, more specific and perhaps less toxic agents.

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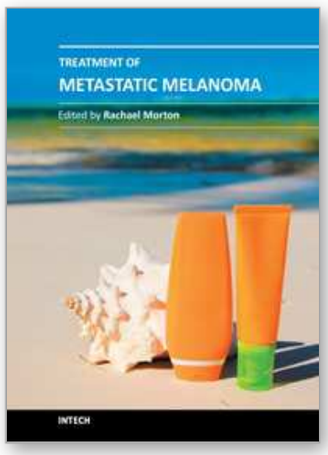

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Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

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