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Review paper

Combination chemotherapy for disseminated malignant melanoma

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Malignant melanoma, once disseminated, is associated with very short survival times and has proven highly resistant to systemic therapy. Although many chemotherapeutic agents can produce small response rates in these patients, the most consistent responses occur with dacarbazine (DTIC). Numerous combination regimens, with and without DTIC, have been tested against disseminated melanoma, with varying and inconsistent outcomes. The most encouraging results have occurred with the combination of DTIC, cisplatin, BCNU and tamoxifen. The use of high-dose chemotherapy with and without autologous bone marrow support and the addition of biologic agents such as inteferon-α and interleukin-2 to conventional chemotherapy have also been actively investigated. This paper reviews the various approaches taken against disseminated melanoma employing systemic chemotherapy.

Key words: Bone marrow transplantation, chemotherapy, cisplatinum, dacarbazine, melanoma.

Introduction

Malignant melanoma, which has demonstrated an exponential increase in incidence over the past 50 years, is a burgeoning public health problem of major proportion. A 1992 estimate projected 32 000 new cases and 6700 deaths per year in the US alone, and it has been predicted that by the turn of the century one out of every 90 Americans will develop the disease.[1,2] Unlike other cutaneous malignancies, it disproportionately afflicts younger individuals; nearly 50% of cases occur in people less than 40, with a median age of 53 years.[1] In spite of its clinical aggressiveness, however, there has been an increase in the 5-year survival rate from 41 to 83%, which is attributed to early detection and surgical excision of early primary lesions.[1] Nevertheless, advanced melanoma retains its poor prognosis and is notoriously difficult to treat. Mean survival is 6 months from diagnosis.[3]

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Single agent experience

As a consequence of disseminated melanoma's poor prognosis, investigators have tried many agents against it, most with disappointing results. The best, most consistent results have come with the use of dacarbazine (DTIC). Since its introduction in the early 1970s, DTIC, administered i.v. for five consecutive days every 3 weeks, has produced an aggregate overall response rate quoted at around 20%, with a median time to progression of 3–4 months and median duration of survival 6–8 months. Tumor regressions have generally been limited to sites of soft tissue involvement. Associated toxicities in-

Table 1. Single-agent response rates in metastatic melanoma[3,4,22]

Single agent	Overall response rate (%)
Dacarbazine (DTIC)	20
Carmustine (BCNU)	18
Lomustine (CCNU)	13
Semustine (methyl CCNU)	16
Chlorozotocin	9
Fotemustine	24
Vincristine	12
Vinblastine	13
Vindesine	13
Cisplatin	15–23
Carboplatin	14–16
Tamoxifen	6
Paclitaxel	15–18
Ifosfamide	11
Mitomycin C	8
Dibromodulcitol	14
Detrorubicin	19

clude nausea and vomiting, myelosuppression, and a flu-like illness.[5]

Other agents with activity against melanoma include the nitrosoureas (BCNU, CCNU and methyl CCNU) and the vinca alkaloids,[6] cisplatin and vindesine,[7] and procarbazine.[8] Although there have been no randomized trials comparing the nitrosoureas, the overall response rate has been about 20%, with advantages over DTIC in that BCNU is administered less frequently (about every 6 weeks) and CCNU is administered orally.[5] McClay and Mastrangelo reviewed promising results with detrorubicin (a semisynthetic anthracycline), paclitaxel, vindesine and dibromodulcitol.[9] Fotemustine has produced encouraging results in several European trials.[3]

Combination regimens

Efforts to improve upon the single-agent response rate of DTIC have resulted in numerous trials of combinations with and without DTIC. The history of combination chemotherapy directed against disseminated melanoma has been described as disorderly;[3] there exists in the literature many single reports of increased antitumor activity, but when regimens are subjected to confirmatory investigation (and comparison to single-agent DTIC), frequently no advantage is found. Creagan[5] has reviewed regional and systemic treatment strategies for metastatic melanoma, as have McClay and Mastrangelo.[9] Creagan observed that occasional reports have indicated approximately 40% response rates for combinations of DTIC and nitrosoureas plus other agents, but these regimens have proven less effective on confirmatory studies. As an example, Creagan cites the experience with vinblastine/cisplantin/bleomycin. This regimen initially gave a 71% overall response rate, which declined to 43% with additional patient accrual, as reported by Nathanson *et al.*;[10] furthermore, in a Mayo Clinic study the response rate to this regimen was just 11%.[11]

In a separate review, Coates observed that systemic therapy using standard agents usually yields reponses below 20%, but he acknowledged that some patients with visceral disease achieve long-term control, measurable tumor response in about 25% of treated patients and perhaps even cure in a small subset of patients.[12] However, he perceived little success with newer agents.

Table 2. Response rates of combination chemotherapy regimens

Combination regimen	Published overall response rates (%)
Dacarbazine-based regimens	
DBPT (Dartmouth regimen)	29–55
dacarbazine/cisplatin	11–77
dacarbazine/tamoxifen	28
CVD	24–45
dacarbazine/vincristine/nitrosourea	20–43
BOLD	4–46
BELD	>40
dacarbazine/dactinomycin	22
Regimens without dacarbazine	
cisplatin/tamoxifen	29–32
procarbazine/vincristine/CCNU	13–60
cisplatin/bleomycin/vinblastine	47
cisplatin/bleomycin/CCNU	48
cisplatin/vindesine/etoposide	31
cisplatin/vindesine/CCNU	20
carboplatin/cytarabine	24

Dacarbazine-based regimens

In 1984, Hill *et al.* published a retrospective review of patients achieving a complete remission in phase III studies conducted by the Central Oncology Group between 1972 and 1976.[13] These studies utilized DTIC alone or in combination with BCNU, CCNU and either vincristine or hydroxyurea. Of 580 patients enrolled on protocols, 24 complete and 86 partial remissions were obtained (two patients with partial remissions eventually converted into complete responses), for an overall response rate of 19%. At the time of study, 18 of the 26 patients who achieved a complete response had relapsed, while six remained in complete remission and two patients had died of unrelated causes. Seven of these patients had received DTIC alone, while 19 received a DTIC combination. Treatment was given for periods ranging from 9 to 215 weeks (median 48 weeks). Remission duration after completion of therapy ranged from 0 to 259 weeks (median 17 weeks). Toxicity was confined to mild myelosuppression and gastrointestinal effects; dose escalation was limited generally because of vomiting and malaise rather than hematologic toxicity. The actuarial probability of persisting in complete remission (relapse-free survival) was estimated to be 19.5% at 72 months, while the actuarial probability of survival was 31.1% at 72 months. There were no significant late deleterious effects observed, and in particular no secondary cancers developed. On the basis of this experience, the authors concluded that melanoma can be cured, 'perhaps, occasionally', and it is on the strength of such experience with DTIC that it has formed the backbone of many of the

published experimental regimens for disseminated melanoma and achieved the status of the standard against which other agents and combinations are compared.

DTIC/bleomycin/cisplatin/tamoxifen (DBPT)

One of the better-known DTIC-based combinations was originally reported by Del Prete and colleagues from Dartmouth University in 1984[14] and consisted of cisplatin 25 mg/m^2 i.v. d1–d3 every 3 weeks, DTIC 200 mg/m^2 i.v. d1–d3 every 3 weeks, BCNU 150 mg/m^2 i.v. d1 every 6 weeks and tamoxifen 10 mg orally twice daily. This study enrolled 20 patients and resulted in four complete responses with two patients alive at 14 and 23 months, one death due to BCNU pulmonary toxicity, and one patient who relapsed at 17 months and died 6 months later. There were also seven partial responses, for an overall 55% response rate. Toxicity included mild to moderate myelosuppression, moderate nausea and vomiting, mild renal insufficiency, and one additional patient with suspected BCNU pulmonary toxicity who resolved radiographic and functional changes. Subsequently known as the 'Dartmouth regimen', this combination generated a great deal of interest in the oncologic community. In a confirmatory study by McClay *et al.*,[15] a 50% response rate in 20 evaluable patients was obtained, albeit without any complete responses; at the time of report, the median duration of response exceeded 7 months. In addition to the toxicities noted by the Dartmouth group, six patients developed deep venous thromboses with four developing pulmonary emboli. This complication raised the question of the role of tamoxifen, particularly since previous published response rates for hormonal therapy were less than 10%. However, when McClay *et al.* attempted to do away with tamoxifen in an additional 20 patients, they obtained just one complete and one partial response, for an overall response rate of 10%, but no thromboembolic complications were seen.[16] The authors stated that this result was statistically significantly worse than the results obtained with the full Dartmouth regimen and theorized that tamoxifen was acting synergistically with other agent(s), possibly via a calcium-channel-blocking effect, and noted this phenomenon had improved responses to cisplatin in experimental models. A follow-up study by this same group re-incorporated tamoxifen into the Dartmouth regimen for 25 additional patients and the response rate returned to 52%, bringing the total response rate in 45 patients treated with tamoxifen to 51%.[17] However, a survival advantage was absent (mean survival 10.8 versus 9.8 months) for tamoxifen. It was hypothesized that this was due to early failure in the central nervous sytem (CNS)—in 48% of responders, the CNS was the first site of the relapse while systemic disease was still responding.

Other groups have attempted to corroborate the favorable response to DBPT. Saba *et al.* reported the University of South Florida experience with a slightly modified Dartmouth regimen in which DTIC was administered as 200 mg/m^2 d1–d3, with cycles repeated every 4 weeks and BCNU repeated every 8 weeks.[18] Of 14 patients, three achieved a complete response and one a partial response, for an overall rate of 28.5% with 48% survival at 300 days compared with 27% of a small control group of six patients. The authors noted that their study population had a higher burden of visceral disease than the Dartmouth group and was also older, and that these differences accounted for the poorer overall response rate. Fierro *et al.* treated 32 patients with the Dartmouth regimen and achieved a 47% response rate (five complete, 10 partial responses) with a median survival for responders of 10 months.[19] Superior responses were seen in women and patients with non-visceral disease. Reintgen and Saba later described 47 patients treated with DBPT, with a 46% response rate (six complete responses).[20] They recommended that DBPT be considered the standard treatment arm of any future protocol for metastatic melanoma.

Nathanson *et al.* recently reported an attempt to substitute megestrol for tamoxifen, at a dose of 160 mg orally once daily starting 2 days after chemotherapy.[21] They obtained a 47% overall response rate (duration 16+ to 108 weeks; median 39+ weeks) with three patients still in remission at time of analysis.

McClay and Mastrangelo have concluded on the basis of the published data that DBPT deserves to be considered front-line treatment for disseminated melanoma, and that tamoxifen plays a key role in producing the favorable responses.[9,22] However, this position has not been universally accepted, as there has not as yet been a trial directly comparing DBPT with DTIC alone.[23]

DTIC/cisplatin

Studies conducted in the 1970s suggested that the combination of cisplatin, which has modest single-

agent activity in disseminated melanoma,[7] with DTIC benefiting some patients, particularly at higher doses.[24] This observation led the Southwest Oncology Group (SWOG) to assess response with DTIC at 750 mg/m^2 and cisplatin 100 mg/m^2 every 21 days.[25] In 30 patients with primary refractory disease they achieved a 37% response rate, with a median duration of 31 weeks. Subsequently, SWOG conducted a larger phase II trial employing the same doses in previously untreated patients and obtained an 11% overall response rate.[26] Toxicity was significant, with 50% experiencing grade III or worse hematologic toxicity and 25% experiencing grade IV toxicity (hematologic, nausea and vomiting, renal). In between these two SWOG trials, a series of reports were published evaluating high-dose cisplatin and DTIC.[27–31] Doses of cisplatin ranged from 150 to 200 mg/m^2 over 3–4 days and DTIC was administered at 1000–2000 mg/m^2 over 3–4 days, both given at 28-day intervals. Overall response rates ranged from 13 to 77%, with the average being approximately 34%. If one discounts the smallest trial in the series,[28] the average response decreases to 23%, which is not notably different from responses obtained with single-agent DTIC, as was observed by several authors.[29,30] Again, toxicities were significant, particularly myelosuppression and nausea and vomiting. Interestingly, tamoxifen was included in one of these trials at a dose of 100 mg twice daily for 7 days, then reduced to 10 mg twice daily.[27] That this modification added little to the regimen was reflected in the 13% overall response rate, although the authors attribute this outcome to patient selection.

Hormonal modulation of DTIC and cisplatin

The apparent synergistic effect between tamoxifen and one or more of the other agents in the DBPT regimen has sparked interest in defining the specificity and mechanism of this interaction. Cocconi *et al.* randomized 117 patients with disseminated melanoma to either DTIC alone versus DTIC plus tamoxifen.[32] Responses were 12 versus 28%, with median survival 29 versus 48 weeks. Superior responses were seen in women (38 versus 10%) in the combined arm, although sex was not a significant discriminator in the single-agent DTIC arm. The authors hypothesized a favorable interaction between DTIC, tamoxifen and endogeneous estrogens in patients with melanoma, and suggested on the basis of their results that DITC plus tamoxifen should become standard therapy for disseminated melanoma. This study was criticized in an accompanying editorial for including patients with local/regional metastases as well as disseminated disease, small patient numbers, maldistribution of prognostic factors and the uncharacteristically poor response rate of single-agent DTIC.[33] The reviewers also noted that little attention was paid to toxicity or quality of life, and there was uncertainty over the doses of DTIC delivered. In a short report published 5 months later, McKeage *et al.* described 16 pretreated patients (14 evaluable) treated with cisplatin and tamoxifen, with or without DTIC.[34] They obtained an overall response rate of 29% and a median survival of 6.4 months, and concluded that these results corroborated those of Cocconi *et al.*

McClay *et al.* approached this issue as a possible interaction between tamoxifen and cisplatin.[35] They treated 24 patients without previous exposure to these drugs with cisplatin 100 mg/m^2 i.v. once very three weeks and evaluated response after each cycle. If disease progressed after one cycle or was stable after two cycles, the investigators added tamoxifen; otherwise the patient was continued on cisplatin alone until achieving complete remission or progressive disease was found. After obtaining just three responses in 24 patients (13%) treated with single-agent cisplatin, 20 patients (19 evaluable) received the combination therapy and there was an overall 32% response rate. For 12 patients who did not respond to the combination or had disease progression, a trial of DBPT produced no responses. The authors concluded that tamoxifen can overcome established resistance to cisplatin in a subset of patients and referred to studies in melanoma cell lines supporting synergy between these agents. A recent article by McClay and McClay reviewed the literature on the use of tamoxifen in melanoma.[22]

Vinblastine or vindesine/DTIC/cisplatin (CVD)

On the strength of DTIC's activity and earlier experience with vinblastine/bleomycin/cisplatin, which was found to produce variable response rates (range 0–43% in several series) hampered by significant toxicity,[10,11] more recent attempts at treating disseminated melanoma have substituted DTIC for bleomycin.[7,36–40] The overall response rate for these trials is 33% (range 24–45%), with median duration of survival ranging from 16–52 weeks. The study providing the longest duration of response

used the highest doses of DTIC (800 mg/m^2 every 3 weeks).[7] Responses were uniformly best in patients with non-visceral involvement. Toxicities included myelosuppression (in some instances severe), nausea and vomiting, peripheral neuropathy, and renal insufficiency. The overall impression for this combination is that of moderate activity producing responses of short duration.

Nitrosoureas plus DTIC and vincristine

Interest in the possible contributions of the nitrosoureas to the management of disseminated malignant melanoma has existed from the earliest days of chemotherapy trials. As single agents, their response rates range from 10 to 20%.[3] In trials conducted in the 1970s, they were frequently combined with DTIC and vincristine to improve response rates; it was also hypothesized by investigators that the characteristically good CNS penetration of the nitrosoureas would benefit patients with CNS involvement. Published reports on this combination show overall response rates ranging from 20 to 43%, but survival was all less than 1 year.[6,41–44] Typically, the best responses were seen in patients with non-visceral disease and patients with CNS involvement consistently had the worst outcomes, in spite of the nitrosourea. Toxicity was largely confined to myelosuppression and emetogenesis. Carmo-Pereira *et al.* recommended this regimen for 'good prognosis patients', meaning women with non-visceral disease.[42] A much later study conducted by Hill *et al.* evaluated the role of dose escalation using DTIC, vincristine and bleomycin versus CCNU, and found no significant difference among the treatment arms, although increasing the dose of DTIC may have increased responses.[45]

BOLD and BELD

In the early 1980s, Seigler *et al.* and Ahn *et al.* reported response rates in patients with disseminated melanoma of 40 and 46% employing BOLD, a combination of bleomycin (15 u i.v. d1 and d4), vincristine (1 mg/m^2 i.v. d1 and d5), CCNU (80 mg/m^2 p.o. d1) and DTIC (200 mg/m^2 i.v. d1–d5), with cycles repeated every 28 days.[46,47] Subsequent attempts at confirmation of these results were not as successful.[48,49] York and Foltz attributed this difference to the more rigorous staging they employed to identify newly-progressive disease in treated patients.[48] Other investigators, noting superior single-agent activity of vindesine as compared with vincristine, substituted vindesine (at 3 mg/m^2 i.v. d1 and d5) into the regimen, rechristened BELD.[50,51] This combination produced response rates in excess of 40% in two small trials, whose authors concluded that the regimen was active against melanoma and better tolerated than BOLD. Toxicities of the two regimens were similar (chiefly nausea and vomiting, with acute reactions to bleomycin in a minority of patients), although BELD produced much less peripheral neuropathy.

DTIC and dactinomycin

Published experience with the combination of DTIC and dactinomycin for melanoma is very limited. Hochster *et al.* treated 21 patients with DTIC 800 mg/m^2 i.v. d1 and dactinomycin 1.2 mg/m^2 i.v. d1, both given every 3 weeks, and obtained a 22% overall response rate, with median duration of 7 months and median survival of 12 months.[52] This activity is indistinguishable from that of DTIC alone. Toxicity was predominantly mild myelosuppression and gastrointestinal upset.

Non-DTIC regimens

Investigators have tried a variety of combination regimens lacking DTIC against melanoma, and there are multiple unique phase II trial reports in the literature. The POC regimen (procarbazine/vincristine/CCNU) has received more attention than most. Carmo-Pereira *et al.* published an initial report on POC in 1980, with a follow-up report in 1984.[8] With additional accrual, their initial 60% response rate fell to 48%, with a median duration of remission of 10 months and median survival of 21 months in responders. Nausea and vomiting were a problem for almost all patients, and some mild myelosuppression was also noted. Shelley *et al.* attempted to confirm these results, but obtained just 13% responses, with an overall median survival of 22 weeks.[53] Their patients experienced much more peripheral neuropathy than had been reported previously. The authors attributed the different outcome from the prior trial to prognostic differences—there were more patients with soft tissue disease in the earlier study and more visceral disease in this study.

Platinum-based combinations, often employing a nitrosourea or vinca alkaloid, have also received some attention. Nathanson *et al.* devised a regimen

of cisplatin, bleomycin and vinblastine for which they reported a 47% response rate exceeding 26 weeks in duration at the time of report.[10] Subsequent attempts by other investigators, including Johnson *et al.*,[54] to corroborate this result were generally unsuccessful. Cohen *et al.* studied a combination of cisplatin, bleomycin and CCNU, and obtained a 48% response rate lasting from 4 to more than 82 weeks in 25 evaluable patients, but this regimen was associated with three treatment-related deaths.[55] A trial conducted by Bajetta *et al.* randomized 37 patients to cisplatin and vindesine with either etoposide or CCNU; response rates were 31% on the etoposide arm and 20% on the CCNU arm.[56] Mulder *et al.* studied a novel combination of carboplatin and cytarabine in 21 patients, obtaining a 24% response rate.[57]

The impression remains that none of these combinations has provided better, more durable responses than single-agent DTIC, and they are frequently associated with greater toxicity.

Bone marrow transplant experience

The resistance of disseminated melanoma to conventional-dose chemotherapy and the frequent occurrence of severe myelosuppression as a dose-limiting toxicity naturally led to investigation into the applicability of high-dose chemotherapy with autologous bone marrow rescue to this disease. The experience to 1989 was summarized by Cheson *et al.* in a large review of autologous bone marrow transplantation.[58] The authors noted the 187 melanoma patients had been treated with single-agent high-dose chemotherapy, usually employing melphalan or thiotepa, with an overall 49% response rate, and 96 patients with high-dose combinations with an overall 61% response rate, all on various studies. Characteristically, responses were of short duration. Fields reviewed the experience in the literature to 1992.[59] Again, relatively high initial response rates can be produced, but disease tends to relapse within a few months of treatment, although a small number of long-term survivors have emerged.

Shea *et al.*[60] enrolled 19 patients with disseminated melanoma in the Solid Tumor Autologous Marrow Program (STAMP) at the Dana-Farber Cancer Institute and Beth Israel Hospital (Boston). These patients received combinations of cyclophosphamide, cisplatin, BCNU and melphalan according to a dose-escalation scheme prior to autologous bone marrow transplant. Twelve of the 20 courses were given as cyclophosphamide 5.625 g/m^2, cisplatin 165 mg/m^2 and BCNU 600 mg/m^2; melphalan at 40 mg/m^2 was administered to one patient and at 80 mg/m^2 to two patients. Melphalan was excluded from the phase II regimen due to unacceptable renal toxicity when it was combined with the other three agents. Seventeen of the 19 patients were assessable for response and a response rate of 65% was achieved, with an overall median survival of 8.6 months (range 0.7–36 months); responders had a median survival of 15.2 months. Two patients were unevaluable due to death from treatment-related complications (CNS hemorrhage, pulmonary hemorrhage and adult respiratory distress syndrome), while two additional patients died after 1 month (cytomegalovirus pneumonia, CNS hemorrhage with thrombocytopenia). Other toxicities experienced included mucositis, infections, impaired hearing and hepatic veno-occlusive disease.

Wolff *et al.*[61] treated 192 patients with high-dose thiotepa (doses ranged from 60 to 525 mg/m^2/day for 3 days). A total of 71 patients with metastatic melanoma were enrolled in this trial and 55 (77%) were evaluable for response. For response evaluation purposes, they grouped patients into three subsets according to cumulative dose: <900 mg/m^2, 900–1125 mg/m^2 and >1125 mg/m^2. Among the melanoma patients, 13 received <900 mg/m^2 of thiotepa and obtained a 41% response rate, while 20 patients were treated at the >1125 mg/m^2 dose level and achieved a 70% response rate. None of these outcomes is statistically significantly different from the others. The median duration of response was 3 months, with a range of 1–31 months. However, the subset of patients receiving the highest cumulative dose (>1125 mg/m^2) experienced excessive skin, mucosal and CNS toxicity, and it was determined by the authors that the maximum-tolerated dose of thiotepa is 1125 mg/m^2. Toxicity was high in this study, with 15 patients dying without tumor progression within 1 month of treatment (two episodes of pulmonary toxicity and 13 episodes of severe infection and/or hemorrhage). Other severe but non-fatal toxicities included mucositis, diarrhea, CNS disturbance and rash, all of which were determined to be dose-related.

Lakhani *et al.*[62] retrospectively reviewed the Royal Marsden Hospital (London) experience treating disseminated melanoma with four different regimens, two of which included high-dose chemotherapy with autologous bone marrow transplant. The high-dose treatments consisted of melphalan at 140–260 mg/m^2 or BCNU at 800 mg/m^2; the other two regimens were BOLD and single-agent videsine, which were not supported with marrow infu-

sion. Nine and 34 patients were treated with high-dose BCNU and high-dose melphalan, with overall response rates of 44.4 and 20.6%, respectively. In this analysis, BOLD produced a 24.4% overall response rate in 31 patients. The median duration of response was 3 months for all regimens. Toxicity on the high-dose treatment arms was severe, with seven patients who received high-dose melphalan dying within 1 month of treatment and one early death among the high-dose BCNU recipients. Nausea, vomiting and alopecia were also observed.

Other therapies

The consistently inadequate response of disseminated melanoma to standard or high-dose chemotherapy has prompted much investigation into alternative treatment modalities. Chief among the alternatives studied have been the biologic agents, including the interferons, of which interferon-α has proven most useful, and interleukin-2.[63] These agents have been employed singly, in combination with each other, and in combination with standard chemotherapeutic agents, including DTIC, vindesine and cisplatin.[64,74] Because single-agent response rates have averaged about 15–20% for either biologic agent, many investigators have attempted combined therapies in an effort to improve upon the responses generated by the chemotherapeutic drugs or biologics alone, often with dramatic results in small phase II trials.[64,66–69,71–74] However, it is generally appreciated that, while response rates can be impressive, there has been little improvement in survival time for the vast majority of patients. In addition, toxicity associated with interferon-α and interleukin-2 has been significant, leading some authors to conclude that their use in combination with standard chemotherapy is too toxic for the marginal benefit derived.[68] Nevertheless, a minority of patients has achieved durable responses, making the continued use of the biologic agents fertile ground for ongoing investigation.

Concluding remarks

Disseminated malignant melanoma remains a difficult, intractable disease. Investigators have tested an array of combination regimens that have shown relatively low overall activity levels, although subsets of patients may respond favorably, most notably women with non-visceral metastases. Patients with liver and particularly brain metastases retain very poor prognoses. Most of these trials have been conducted in a phase II setting; very few prospective randomized trials have been reported, especially phase III trials comparing these combinations to DTIC alone, which continues to represent the standard against which combination regimens should be compared. The DBPT and CVD regimens have fairly good, reproducible response rates and acceptable toxicities, and are reasonable options for patients off protocol, but are not yet proven superior to DTIC alone. The contribution of other therapeutic modalities, such as bone marrow transplant and the biologic agents, remains to be defined. Several investigators have recommended that whenever possible, patients should be enrolled on prospective randomized trials; alternatively, single-agent therapy with DTIC or a nitrosourea should be offered.[5,12]

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