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Original Article

The current role of systemic therapy in the management of Malignant Melanoma of the skin: a literature review

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Abstract

Melanoma patients can be split into two main categories that have different aims for treatment; localised disease with either intermediate or high-risk of recurrence after surgery, and metastatic disease. Over the past decade, there have been many clinical trials looking at improving the success rates for localised and metastatic melanoma with alternative systemic treatments, namely immunotherapy, biochemotherapy and vaccines. This literature review summarises the clinical trials for each form of systemic treatment in localised and metastatic melanoma and assesses the effectiveness of each by an evaluation and comparison of relevant clinical trials for each systemic modality. The main objective was to assess whether alternative forms of systemic therapy have improved the disease free and overall survival rates achieved with chemotherapy.

Keywords

Melanoma; immunotherapy; vaccine; chemotherapy; surgery; interferon; interleukin

INTRODUCTION

Malignant melanoma (MM) comprises only 4% of all skin cancers. However, the incidence of melanoma is increasing at a faster rate than of any other tumour.[1] Localized MM is highly curable with roughly 80–90% of people surviving post 5 years of diagnosis.[2a] Whilst efforts to increase early diagnosis through education have increased detection of early-stage melanoma, many patients still present with advanced disease. Once melanoma metastasises, the prognosis is much poorer as the 5 years survival rate falls to only 20–30% and life expectancy to only 6 months.[2a] Melanoma patients are split into two main categories that have different treatment aims; localised disease with either intermediate or high-risk of recurrence post-surgery, and metastatic disease. This paper will consider both groups individually.

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Localised disease

Surgical excision has 92–96% survival rates,[3] which rapidly decrease once vertical invasion establishes due to high-risk of recurrence, e.g. the nodal metastasis rate for lesions measuring less than 1.5 mm and greater than 4.0 mm is 7% and 30%, respectively.[4] Nodal status is an excellent prognostic indicator, as 5-year disease free survival (DFS) reduces from 85% to 40% with positive lymph nodes.[5] Intermediate/high-risk patients (T1–4N1M0, American Joint Committee on Classification (AJCC) Stage II/III) (Table 5)[134] are

candidates for adjuvant therapy to reduce the risk of recurrence from residual metastases.

Up to 75% of patients with MM develop brain metastases, for which the outlook is poor. Radiotherapy is the current standard of palliative care however, whilst it can improve neurologic symptoms it does not alter disease outcome. Objective responses are rarely observed with systemic therapy, and median survival is short.[135,136] This lack of efficacy could be related to the inability of most chemotherapeutic and biologic agents to penetrate into the CNS. Two new agents, Temozolamide and Fotemustine, are currently under investigation.

Metastatic disease

Treatment is administered with the aim of improving patients' quality of life (QOL) and in some cases prolonging survival. 10–50% 5 years survival rates are reported with complete resection.[6] However this is rarely achieved and most patients are unsuitable for surgery.

Numerous systemic treatments are available for the two patient groups. The aim of this literature review is to evaluate current systemic treatments in the management of MM by appraising clinical results.

METHODOLOGY

Search terms used to retrieve all available literature and to provide a clear search focus. The medical databases MEDLINE, SCIENCEDIRECT, CINAHL, EMBASE and CancerLit, were used as it was anticipated that these would retrieve all available papers. References of relevant papers and books were reviewed to identify additional articles. If more than one report was found for a trial, the most recent was used unless results were reported more comprehensively in the earlier report. Clear inclusion criteria were applied to determine eligible literature:

1. Papers related to chemotherapy or immunotherapy for metastatic disease had to be published from late 1980's onwards. This was to ensure inclusion of the findings in these fields from trials that were largely conducted around this time period.
2. Papers could be from any country to ensure inclusion of all relevant research. The limitation was that they had to be published in English, due to translation difficulties.
3. The papers were to be randomised controlled trials (RCTs) although preliminary research indicated that few RCT trials have been undertaken for certain agents e.g. vaccine therapy. In these cases, non-randomised studies were accepted.

Trials were critically analysed using the following research questions.

Localised melanoma

1. What are the response rates (RR) and disease-free survival and how do these compare to control groups (if available), and other forms of systemic treatment?
2. How is the overall survival (OS) affected by any changes in disease-free survival or relapse rates?

Metastatic melanoma

1. What are the response rates and how do they compare to control groups (if available), and other forms of systemic treatment?
2. Has the overall survival of the patients been increased?

CHEMOTHERAPY

Localised melanoma

Only isolated-limb perfusion (ILP) chemotherapy (Melphalan) RCTs was identified. ILP had no effect on OS for intermediate/high-risk melanoma post-surgery. Agents are only delivered to the extremity of the patient therefore it is questionable whether ILP can be expected to reduce the incidence of systemic metastases.[7] A meta-analysis was unsuitable, as results would be unduly influenced; 80% of patients were treated in one of four RCTs.[8–11] Significant differences between the clinical trials require further, homogenous RCTs for a valid assessment of ILP for these patients.

Metastatic disease

Dacarbazine (DTIC) is considered the "gold standard" in single-agent chemotherapy of metastatic

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Table 1. Response rates for metastatic melanoma with single-agent chemotherapy

Agent	Response rate (%)
Dacarbazine (DTIC)	15–20
Nitrosoureas	10–20
Carmustine (BCNU)	
Lomustine (CCNU)	
Vinca alkaloids	10–15
Vinblastine	
Vindesine	
Cisplatin	15–20
Taxane	15–19
Paclitaxel	
Docetaxel	
Tamoxifen	6

Table 2. Response rates for MM with combination chemotherapy from randomised trials

Regimen	Number of patients	Overall response rate (%)	Median survival (months)
CVD vs DTIC			
Buzaid (1993)[5b]	120	24 vs 11	7 vs 5
BCDT vs DTIC			
Rusthoven (1996)[40]	106	30 vs 21*	7
Johnston (1998)[80]	30	27 vs 23**	5.5 vs 5.0
Sileni (2001)[128]	39	22 vs 19	8.0
Saxman (1999)[129]	240	17 vs 9.9	7.7 vs 6.3
Chapman (1999)[130]	240	18.5 vs 10.5	7.7 vs 6.4
Tamoxifen-based			
Cocconi (1992)[37]	52 vs 60	12 vs 28	6 vs 11
Legha (1993)[38]			
PVD + IFN	36 vs 33	47 vs 30	9 vs 10
−/+ TMX			
Ferri (1999)[39]			
C + D −/+ TMX	29 vs 27	10.7 vs 14.3	7 vs 4.6
Rusthoven (1996)[40]			
BDP −/+ TMX	97 vs 98	21 vs 30	10 vs 9
Falkson (1998)[41]			
DTIC −/+ IFN	68 vs 65	15 vs 21	8.7
−/+ TMX	63	18	8.9
−/+ IFN & TMX	67	19	9.0
Creagen (1999)[131]			
CDB −/+TMX	184	33 vs 27	6.8 vs 6.9

*, **, *** = Although these were randomised, double blind trials, they compared response rates and survival of patients who received the Dartmouth regimen with TMX or with a placebo; with IL-2; with Interferon (IFN), respectively, and not against DTIC alone as in the other trials; D = dacarbazine; TMX = tamoxifen; P = cisplatin; V = vinblastine; IFN = Interferon alpha; C = carboplatin; B = carmustine; ND = not determined; NS = not significant; NR = not recorded

melanoma. Overall RRs are consistently between 15–25%, however the 4.5–6 month OS is not an improvement on life expectancy without treatment.[2] Other single-agents including Tamoxifen, Nitrosureas, Platinum compounds; Vinca-alkaloids and Taxanes have not improved the clinical outcome.[12–31] In conclusion, several chemotherapeutic agents have modest activity in metastatic melanoma (Table 1) though none demonstrate consistently increased OS or RR greater than 25%.

Combination regimens have demonstrated minimal RR improvement (20–30%) in Phase II trials.[32–36] The most active are CVD (Cisplatin, Vinblastine and DTIC), tamoxifen-based and BCDT "Dartmouth" (Carmustine, Cisplatin, DTIC and TMX), however subsequent Phase III trials have not confirmed a significant RR or OS improvement[40,80,128–130] (Table 2) and all reported increased toxicity with combination regimens.

The addition of TMX to DTIC demonstrated a statistically significant improved RR and OS in the first RCT (28% vs 12%, P = 0.03, 48 weeks vs 29 weeks, P = 0.02).[37] Again, subsequent trials did not confirm this, although in most cases the RR's were comparable if not higher than DTIC alone.[38–41,131]

IMMUNOTHERAPY

Interferon alpha (IFNα)

IFNα has been extensively studied for intermediate/high-risk and metastatic patients due to its range of anti-proliferative and immunomodulatory properties.[42]

Intermediate/high-risk patients

Clinical trials have evaluated low (LDI), intermediate (IDI) and high-dose (HDI) IFN regimens for intermediate (AJCC II, Breslow thickness ≥0.75 mm and without clinically apparent regional lymph node disease), and high-risk (AJCC III+, Breslow thickness ≥1.5 mm with/without clinically apparent regional lymph node disease) patients.

Low-dose IFN

LDI does not achieve durable (curative) responses for intermediate or high-risk disease, as there is an inconsistent impact on OS.[43–45,49–52] Rusciani[47] subdivided patients receiving LDI according to

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clinical stage (Stage I/II) and Breslow thickness. LDI was most effective for patients with thick melanomas after both 3 and 5 years follow-up, but did not significantly alter the risk of progression for thin melanomas. This type of melanoma showed a trend towards late development of metastatic disease (even 10 years post-detection) in comparison with thick melanoma, which has the highest incidence of recurrence during the first 2 years.[48] This advocates applying long-term and short-term schedules, respectively, although further studies with longer follow-up are required to confirm this.

Intermediate-dose IFN

The only RCT of IDI for high-risk patients employed an induction period of 4 weeks followed by a maintenance period of either 10 MU (1 year) vs 5 MU (2 years).[53] The results indicated that treatment duration was important, since only the longer regime had any impact on the primary endpoint of distant metastasis-free interval ($P = 0.0145$).

High-dose IFN

HDI appears to have a benefit for high-risk melanoma patients. Two RCTs[54,55] reported significantly greater DFS (2.4 years vs 2.0 years, $P = 0.19$ and 1.72 years vs 0.98 years, $P = 0.0023$, respectively) and OS rates (4.1 years vs 2.7 years, $P = 0.44$ and 3.82 years vs 2.78 years, $P = 0.0237$, respectively) after ~6.5 year median follow-up. A mature update of the latter study[56] at 12.6 years indicated that only the DFS advantage persisted, however, this could be attributed to the fact that participants were 70+ years. The subsequent Eastern Cooperative Oncology Group (ECOG) 1690 trial[57] again reported an early significant DFS benefit for HDI compared to observation (44% vs 35%, $P = 0.054$) though no significant long-term survival benefit (52%, 55%, respectively at 5 year follow-up). It should also be noted that 31% of observation patients who relapsed in the E1690 trial were non-randomised to receive IFNα salvage therapy, which could have prolonged OS in a supposed observation control group.

The E1694 trial[58] reported a significant increase in 2 year DFS (62% vs 49%, $P = 0.0015$) and OS (78% vs 73%) from HDI compared to a GM2 vaccine. However this was after an inconsequential median 16-month follow-up in comparison to other studies. The authors did not employ a control arm and a pooled analysis of E1694, 1690 and 1684 observation control patients showed that the GM2 vaccine recipients had an improved outcome and were not a valid substitution for observation control arms.[59]

The results for intermediate-risk patients are inconsistent and do not support the use of HDI. As observed previously, HDI had a significant impact on DFS but not OS at early analysis in the inter-group 1694 trial.[58] Subsequent ECOG 1684 and 1690 trials demonstrated no significant impact on DFS or OS[55,57] and the NTCCTG trial HDI actually had a negative impact on both.[52]

An alternative form of IFN, IFNγ, was investigated in one randomised trial for resected Stage II/III (AJCC) patients.[60] But IFNγ did not improve either DFS or OS after a 2.5 years follow-up (DFS 64% vs 66%; OS 79% vs 89%).

Metastatic disease

IFNα has only been investigated for metastatic disease in small Phase II trials. The overall ~15% RR is comparable with single-agent chemotherapy though some trials[61–63] reported significantly higher at between 25–38%.

Interleukin-2

IL-2 has various anti-tumour mechanisms including cytotoxic T- and natural killer cell activation and production of other cytokines.[64] Non-randomised trials for metastatic melanoma have reported comparable RRs (15–20%) to DTIC though with some long-term survivors (~10% of responding patients lived beyond 5 years).[65–67] A systemic review of single-agent IL-2 trials reported a similar result but was exclusively based on non-randomised trials using a wide-range of dosing schedules/administration, which could explain the variable RRs (3–50%).[68]

Interleukin-2 + IFNα

Initial Phase II trials of IFN + IL-2 appeared encouraging with 20–40% RRs for adjuvant therapy of resected disease. However, subsequent RCTs (Stage II and advanced disease) reported disappointing 5–10% RRs and no survival advantage.[69,70]

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Table 3. Response rates for MM with biochemotherapy from randomised trials

Study	Number of patients	Overall response rate (%)	Overall survival (months)
Kirkwood (1990)[132]	45	19/24	Terminated early
Falkson (1991)[71]	61	20/53	2.5/8.9
Thomson (1993)[133]	170	17/21	8/9
Bajetta (1994)[74]	242	20/25	11/12
Falkson (1995)[72]	73	20/50	8/16.7
Falkson (1998)[41]	258	15/21	10/9.3
Young (2001)[76]	61	50	4.8
Keilholz (1997)[78] Il-2&IFN −/+ C + Il-2/IFN	138	6/5	9
Johnston (1998)[80] BCDT −/+ IL-2 & IFN	65	0/3	5.5/5.0
Rosenberg (1999)[84] CDT −/+ IL-2/IFN	102	8/6	15.8/10.7
Dorval (1999)[79] C & IL-2 −/+ IFN	101	6/4	10.4/10.9
Eton (2000)[82] CVD −/+ IL-2 & IFN	183	25/48	9.2/11.9
Hauschild (2001)[81] DTIC & IFNα −/+IL-2	281	8.3/7.3	11/11
Ridolfi (2001)[83] CD (optional carmustine) −/+ IL-2 & IFN	176	16.7/14	9.5/11

BIOCHEMOTHERAPY

IFNα + chemotherapy

Two trials[71,72] reported significantly increased RRs and OS (both 53% vs 20%, and 9 months vs 2.5 months and 16.7 months vs 8 months, respectively) with the addition of IFN to DTIC for metastatic disease (Table 3). However, further trials failed to confirm this[73–76]; in fact the RR and OS was lower in the combination arm (18% vs 23%, 4.8 months vs 7.2 months) in the latter trial. This trial however was stopped early because of recruitment difficulties. In addition, the survival analysis included two patients unfit to receive treatment and only 28% of patients completed the full-intended treatment.

IL-2 + chemotherapy

The most investigated combination, of IL-2 and DTIC, has yielded 22–26% RRs and 9.5-month OS in Phase II studies which again is not significantly different from DTIC or IL-2 alone and the combination regimes were definitely more toxic.[77] However, the chemotherapy and IL-2 regimens varied enormously and results have not been confirmed in RCTs.

Various regimes have been studied in RCTs[78–84] (Table 3) although only two demonstrate an advantage. Eton[82] compared an intensive sequential (CVD + IFNα + IL-2) regime versus outpatient CVD alone. The results were very promising as a significantly superior RR (48% vs 25%, $P = 0.001$) and OS (11.9 months vs 9.2 months, $P = 0.05$) for biochemotherapy was reported which few other biochemotherapy regimens achieve. RRs were almost doubled in the second trial[84] using sequential CDT (Cisplatin, DTIC and TMZ), IFNα and high-dose IL-2 (44% vs 27%, $P = 0.071$). Interestingly there was a slight improved survival trend in the chemotherapy arm (15.8 months vs 10.7 months, $P = 0.052$). It is unusual that a regimen with a higher RR and without a high mortality rate would have an adverse impact on survival. This unusual finding may have arisen because a high-dose IL-2 therapy crossover was allowed for patients treated with chemotherapy alone. Further possible explanations include small patient numbers, imbalances between treatment arms (a higher proportion of patients with a poorer performance status and multiple metastases in biochemotherapy arm) and the study was not powered for a survival analysis.

VACCINES

The aim of vaccines is to increase the immunogenicity of tumour-associated antigens since it is believed that these are often too weak to induce active immune responses.

Univalent vaccines

Gangliosides are antigens anchored to the cell membrane that are over-expressed, particularly on melanoma cells.[85] In a double blind RCT[86] 122 patients (AJCC Stage III) were treated post-surgically with either the ganglioside vaccine mixed with Bacille Calmette-Guerin (BCG) or BCG alone with low-dose Cyclophosphamide. More vaccinated patients developed GM2-antibodies (86% vs 11%) and this appeared to correlate with a significant increase in DFI and OS

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(23% P = 0.02 and 14% P = 0.15, respectively) at 51 months. A later RCT[87] of the vaccine linked to a carrier protein, KLH +/− IFNα for Stage IIB or III disease demonstrated an early significant survival benefit with adjuvant IFNα.

Various melanoma peptide antigens have been identified, including tyrosinase, gp100 and MART1. At present only Phase I trials have administered peptide vaccines in various formulations.[88–93] Tumour cells can express multiple tumour antigens therefore multiple-antigen vaccines are proposed to be more effective though to date, they have only been tested in small murine/in vivo studies or studies of small numbers of advanced melanoma patients.[94–95] Various methods to augment the antigen-specific immunity of peptide vaccines are employed. Antigenic peptides have been directly loaded onto dendritic cells (DCs) with a promising 31% RR.[85] Weber[96] immunised 48 resected Stages IIA and IIB patients with two tumour-antigen peptides (gp100 and tyrosinase) +/− the addition of a growth factor, GM-CSF in a randomised Phase II trial. However, the study was not designed to formally establish a statistically significant increase in immune effect with GM-CSF. Any conclusions are precluded as the OS and RRs are not reported for each trial arm.

Rosenberg[88] altered the sequence of a synthetic gp1000 peptide vaccine administered to metastatic melanoma patients post-surgery +/− high-dose IL-2. The unmodified vaccine failed in most cases to elicit T-cell responses, whereas the modified vaccine induced T-cell responses in 91% of cases, but interestingly, no clinical responses. The administration of high dose IL-2 following modified peptide vaccination reduced T-cell responses to 16% but in these patients, a unexpectedly high clinical RR of 42% was seen (Table 4) which is a significant improvement over high-dose IL-2 alone. A multi-institutional clinical trial[97] randomised advanced melanoma patients to modified gp100 vaccine +/− high-dose Il-2 is awaited with anticipation due to the previous promising results.

Table 4. Clinical and host responses to gp100 peptide vaccines in metastatic melanoma (Rosenberg 1998)[88]

Vaccine	Number of patients response (%)	Clinical response (%)	Host cytolytic T-cell response (%)
gp100	9	11	25
Modified gp100	11	0	91
Modified gp100 + IL-2	19	42	16

Polyvalent vaccines

Polyvalent vaccines are made from whole melanoma cells and are subdivided into either allogeneic or autologous vaccines.

Allogenic

Allogeneic tumour vaccines contain multiple antigens shared among large numbers of patients and can therefore induce antibody responses to several melanoma antigens.[98,99] Morton and colleagues[100] developed a polyvalent vaccine (CancerVax) in the hope that this would be more immunogenic and clinically effective. In Phase II trials with metastatic melanoma patients[100,101] the CancerVax vaccine yielded an overall RR of 15–20% and a significantly improved OS compared to non-vaccine therapy historical controls (23 months vs 7.5 months, P = 0.0001). Vilella[102] treated twenty-eight Stage III/IV melanoma patients with a similar polyvalent vaccine and again yielded a promising 26% 20.2 month OS particularly given the very poor patient prognosis.

Another vaccine, Melacine, induced 19% RR in 106 advanced patients with a substantial OS of over 36 months; four patients receiving vaccine maintenance treatment were still alive 6–9 years later.[103] This apparent survival advantage has also been reported for resected Stage III patients (50% relapse-free after three-years).[104] The only Phase III trial of Melacine or observation (post-surgery) in 689 Stage II patients[105] reported no significant DFS or OS improvement.

Melacine has been compared with standard four-drug chemotherapy (DTIC, Cisplatin, Carmustine and Tamoxifen) in a Phase III RCT trial in 140 Stage IV patients.[106] The RR was actually higher in the chemotherapy arm (28% vs 6%) but there was no significant difference in OS (12 months vs 11 months).

Another allogeneic vaccine, Vaccinia Melanoma Oncolysate, had a promising 33% RR in Phase II

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Table 5. *TNM, AJCC and Breslow thickness staging systems*

AJCC	TNM	Characteristics
I – Primary tumour thickness <1.5 mm with no regional lymph node or distant metastases	Tis – Melanoma in situ	Localised disease
IIA – Primary tumour thickness 1.5–4 mm with no regional lymph node or distant metastases	T1 – Tumour 0.70 mm or less and invades papillary dermis	
IIB – Primary tumour thickness >4 mm with no regional lymph node or distant metastases	T2 – Tumour >0.70 mm but not more than 1.5 mm and/or invades papillary-reticular dermal interface T3 – Tumour >1.5 mm but not more than 4 mm in thickness and/or invades reticular dermis T4 – Tumour >4.0 mm thickness and/or invades subcutaneous tissue and/or satellites within 2 cm of primary	
III – Any primary tumour with lymph node metastases but no distant metastases	N1 – Metastases ≥3 cm in greatest dimension in any regional lymph node(s) N2 – Metastases >3 cm in greatest dimension in any regional lymph node(s)	Palpable regional lymph nodes
IV – Any primary tumour with lymph node or distant metastases	M1 – Distant metastases M1a – Metastases in skin or subcutaneous tisssue or lymph node(s) beyond regional lymph nodes M1b – Visceral metastases	Presence of distant metastases

Breslow thickness (four categories of tumour thickness):
- 0.75 mm
- >0.75 – 1.5 mm
- >1.5 – 4.0 mm
- >4.0 mm

trial with advanced patients,[107] and led to a statistically significant increase in DFS and OS in high-risk Stage I/II patients post-surgery.[108,109] However, two further Phase III RCTs did not confirm a benefit for high-risk patients.[110,111]

Autologous

Autologous tumour cell vaccines contain antigens unique to an individual's melanoma to produce increased immunogenicity.[112] Early attempts had little success[113,114] therefore subsequent studies adopted various immunologic adjuvants to increase tumour immunogenicity e.g. GM-CSF, dinitrophenyl (DNP). Three Phase I/II trials, including a total of 119 metastatic patients, reported disappointing RRs of 6–20%.[115–117] The researchers hypothesised that, as in other immunotherapies, the clinical effectiveness was limited by tumour burden. Subsequent trials tested the vaccine post-surgery for a total of 110 Stage III/IV patients.[118,119] Substantial DFS (17–35 months) and OS (~63 months) were reported in patients who attained anti-melanoma reactivity.

Cytokine gene-modified tumour cell vaccines (GMTV)

The main concept behind GMTV is the transduction of genes encoding immunostimulatory cytokines e.g. IL-2/6/7, IFNγ and GM-CSF, into tumour cells to enhance tumour immunogeneicity without causing systemic toxicity.[120] A number of Phase I/II trials[114,120] with GMTV for advanced melanoma have failed to mediate clinical tumour responses. However the results are predominately from a few Phase I trials therefore further Phase I/II trials are required to form a solid conclusion.

DISCUSSION

The aim of the literature review was to evaluate the current role of systemic treatments in the management of MM. Single-agent/combination chemotherapy or immunotherapy alone has not produced RRs high enough to affect OS. Limited Phase II trials suggest that IL-2 could be of benefit to the limited number of patients that experience significant long-term survival.[121] It is difficult to draw firm conclusions due to the short-term follow-up and uncertainty due to bias selection of higher prognostic patients. Randomised trials are required to confirm results and identify subgroups

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most likely to experience long-term survival as the significant toxicity of IL-2 prevents a selective approach.

Some biochemotherapy regimens have marginally increased RRs, and in certain cases OS to up to 12 months. However this has been at the expense of significant toxicity that can seriously affect patients' QOL.[122] Since the aim of palliative treatment is to improve QOL, "numerical" RR and OS improvements that entail significant toxicity and hospital admission may not be acceptable.

Most metastatic melanoma patients eventually die of brain metastases. Cytotoxic agents have limited efficacy for CNS metastases due to an inability to cross the blood-brain barrier therefore this group of patients are excluded from most studies. Two main agents, Temozolomide and Fotemustine, have been investigated for the prevention and treatment of CNS metastases.[125,126] These agents appear to be as active as DTIC, however, further RCTs (including patients with brain metastases) are required to draw strong conclusions as in the first trial, patients most likely to demonstrate a statistical advantage, were excluded.[125]

IFNα has shown reproducible efficacy in patients following resection for high-risk melanoma. A meta-analysis of RCTs comparing IFNα with observation[123] reported a highly significant 17% reduction in the chance of recurrence ($P = 0.000003$) but a less significant 3% survival benefit ($P = 0.1$). At present, only HDI has demonstrated this benefit and this does not apply for other IFNα doses or intermediate-risk disease. Observation post-surgery appears to be the best option for intermediate risk disease at this time.

The rebound in relapse rates lead to the hypothesis that IFNα needed to be administered for long periods of time to impact upon OS.[43–45,53] These results support the ongoing EORTC 18991 trial evaluating the impact of long-term (5-year) maintenance IFN compared to observation in 900 Stage III patients.

There would probably be little debate about adjuvant HDI for high-risk melanoma was it not for the significant toxicity. ECOG grade 3 and 4 toxicities were noted in around one-third of patients, but were rapidly reversible on cessation or dose-reduction (33–58%). The question is whether increased DFS justifies the significant toxicity. Any informed decisions must take QOL into consideration, but few clinical trials do (for all treatment modalities). The E1684 trial QOL study indicated that patients gained a mean 8.9-DFS months and 7 months of OS with HDI. The HDI group experienced a mean of 5.8 months without treatment-related toxicity thus enjoyed more QOL survival time than the observation group. It is notable that HDI-treated patients rated the QOL associated with recurrence much lower than even severe treatment-related toxicity, which would appear to support HDI. However the analysis was conducted retrospectively and there was no re-analysis against updated follow-up of this trial at 12.6 years[55] or the subsequent E1690 trial in which OS improvement was not reproduced.

The major problem of HDI therapy is the necessity to treat all patients due to difficulties in identifying those at highest risk of disease-progression. Further research is required to define prognostic models to select patients most likely to respond. One prognostic factor highlighted by this review has been nodal involvement. In the NCCTG trial,[52] there was significantly greater DFS (17 vs 10.8 months in control group $-P = 0.04$) and trend toward improved OS (47% vs 39% at 5 years, OS = 4.1 years vs 2.7 years $-P = 0.44$) for Stage III, node-positive patients. The ECOG 1684 study confirmed the benefit in node-positive patients with a doubling of DFS and an increase of OS from 30–42%.[55] Unlike the NCCTG study,[52] a larger percentage of patients (89%) had node involvement but the small size of the node-negative subgroup ($n = 31$) makes it difficult to determine whether there is truly an advantage for node positive patients.

Vaccine therapy is particularly attractive because of the minimal, local side effects. To date, no large, RCT has demonstrated an OS improvement. It is difficult to determine vaccines' benefit due to the lack of properly designed Phase III trials. Certain Phase III trials compare results against historical control arms. Selection bias could be introduced as control arm patients were retrospectively

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selected. Also, some supposed control arms included patients receiving additional agents suggested to have anti-tumour activity.[86]

LIMITATIONS OF STUDY

A meta-analysis provides a more precise evaluation of treatment effects in pooling trial data[124] but was not conducted due to the limited RCT data and since the broad study is unsuitable for an overall meta-analysis. Results from other meta-analyses were utilised to supplement the literature review.

Seven non-English papers were excluded due to linguistic limitations. It is possible that these papers held results that could alter the relative perception of a systemic treatment modality. The researcher deemed this effect to be minimal due to the relatively small number excluded.

Fourty-five non-randomised trials (mostly phase I/II) were excluded where randomised phase III trials were available. They contain a substantial quantity of data on systemic treatments for MM patients (who often don't progress to inclusion within Phase III trials), though it is difficult to draw firm conclusions due to the possibility of bias selection of higher prognostic patients and a thorough data analysis/meta-analysis of the results cannot be conducted.

Some trials appear to have sample sizes calculated on unrealistic outcome differences e.g. the EORTC study was powered to detect a 100% improvement in OS from 12–24 months, although this was not achieved in any other treatment trials.[78]

CONCLUSION

Despite the availability of several chemotherapeutic and immunomodulatory systemic agents, we are yet to see survival advantages in either the metastatic or adjuvant setting. Only biochemotherapy regimes have demonstrated increased RRs, and in some cases OS, within RCTs for metastatic disease. This combination is now commonly used, though at the expense of significant toxicity. Patients selected for treatment should be those most likely to experience significant survival benefit to justify the toxicity. Future trials should incorporate QOL assessments to ensure that the most appropriate modalities are used for palliation. Public awareness campaigns should be encouraged to increase detection of early-stage disease due to the lack of effective therapies for advanced melanoma.

HDI demonstrates significant benefit in reducing relapses for high-risk patients. The advantage of HDI is based on indirect comparisons of IFNα-dose groups in different trials. Study population and administration schedule differences could affect this analysis therefore more randomised dose comparisons are required as only one such trial was available.[57]

Further research is required to confirm if node-positive patients are most likely to respond to HDI. If confirmed, accurate nodal status staging will be essential to identify nodal involvement. One such diagnostic method under investigation is sentinel lymph node biopsy.[46,127]

To date, no vaccine has proven to have a definite role in the treatment of melanoma. The common conclusion drawn from the studies is that vaccines have been largely ineffective in advanced patients and appear to have most impact on survival when there is minimal tumour burden in the adjuvant setting. However this has only been investigated in a handful of trials to date and should be followed up. Vaccines could offer an alternative to more toxic systemic treatments if reliable and sufficiently strong immune responses could be maintained.

Most trials for metastatic melanoma include patients that have already received treatment before. This could increase the chance of drug resistance (particularly if patients were refractory to agent/s first time round). However, it would be difficult to exclude these patients due to present trial recruitment problems. One solution is to perform a retrospective sub-group analysis, applied in few trials at present.[52,75]

A lack of Phase III RCTs for all systemic treatments leads to a concern that clinicians make informed decisions on treatments largely based on Phase II trial data. RCTs with sufficient power to

detect a benefit are often not achievable due to trial recruitment. Metastatic patients often have too poor a performance status to participate within trials that can have significant side effects, and those that do often do not complete the intended courses of treatment. Multi-institution trials should be encouraged to assimilate small groups of recruited patients from separate institutions and to encourage standardisation of drug schedules. This should enable further meta-analyses to be conducted to render greater power in results by aggregating small samples for analysis.

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