Chemosaturation with percutaneous hepatic perfusion of melphalan for metastatic uveal melanoma

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Uveal melanoma, the most common primary ocular malignancy in adults, carries a poor prognosis: 50% of patients develop the metastatic disease with a 10–25% 1-year survival and no established standard of care treatment. Prior studies of melphalan percutaneous hepatic perfusion (M-PHP) have shown promise in metastatic uveal melanoma (mUM) patients with liver predominant disease but are limited by small sample sizes. We contribute our findings on the safety and efficacy of the procedure in the largest sample population to date. A retrospective analysis of outcome and safety data for all mUM patients receiving M-PHP was performed. Tumour response and treatment toxicity were evaluated using RECIST 1.1 and Common Terminology Criteria for Adverse Events v5.03, respectively. 250 M-PHP procedures were performed in 81 patients (median of three per patient). The analysis demonstrated a hepatic disease control rate of 88.9% (72/81), a hepatic response rate of 66.7% (54/81), and an overall response rate of 60.5% (49/81). After a median follow-up of 12.9 months, median overall progression-free (PFS) and median overall survival (OS) were 8.4 and 14.9 months, respectively. There were no fatal treatment-related adverse events (TRAE). Forty-three grade 3 (29) or 4 (14) TRAE occurred in 23 (27.7%) patients with a significant reduction in such events between procedures performed in 2016–2020 vs. 2012–2016 (0.17 vs. 0.90 per patient, $P < 0.001$). M-PHP provides excellent response rates and PFS compared with other available treatments, with decreasing side effect profile with experience. Combination therapy with systemic agents may be viable to further advance OS. *Melanoma Res* 32: 103–111 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Background

Uveal melanoma (UM) is the most common primary ocular malignancy in adults with marked differences to cutaneous melanoma (CM) in terms of clinical behaviour, response to treatment, and mutation profile [1,2]. There has been significant progress in the understanding of UM biology [2–4] but primary disease treatment advances have not translated into improved survival [5], with liver metastases being the key determinant of overall survival (OS) [6]. Up to 50% of UM patients develop metastatic UM (mUM) [7], with a poor prognosis and 1-year survival of 10–25% [8]. The liver is the most frequently (>85%) involved and in ~50% of patients, the only site of metastatic disease [6].

Current systemic treatments for mUM have poor response rates (<20%), especially in those with progressive hepatic disease [9]. This appears to hold true even for the newest systemic immunotherapy agent, tebentafusp (IMCgp100), a first-in-class immune-modulating T-cell receptor against cancer [10].

Melphalan percutaneous hepatic perfusion (M-PHP) was devised using the principle of altered blood supply to tumours vs. liver parenchyma in a similar manner to surgical isolated hepatic perfusion (IHP). Compared to IHP, M-PHP has the advantages of being less invasive, the possibility of repeat intervention, and reduced morbidity and mortality. Phase I [11] and phase III [12] trials demonstrated the feasibility of treatment and significantly improved hepatic and overall progression-free

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survival (hPFS and PFS) vs. best alternative care. Technological refinements, such as improved melphalan filtration, have helped to minimize the side effect profile of the procedure [13].

To date, the handful of M-PHP studies reported in the literature have been limited by small sample sizes, whereas studies across both liver-directed and systemic treatments for mUM suffer from large variations in patient selection criteria and design. In a recent meta-analysis, Rantala *et al*. [14] provided criteria to maximize the comparability of analyses despite the limitations of any given study (Supplementary Material 1, Supplemental digital content 1, *http://links.lww.com/MR/A286*) and we adhere to these in this study.

The aim of this retrospective cohort study is to evaluate the safety and efficacy of this intervention in the largest number of mUM patients treated in a single centre with M-PHP to date worldwide.

Materials and methods

Patient selection

All patients with histologically confirmed mUM who underwent M-PHP in our institutions between August 2012 and September 2020 were included in this retrospective study (Fig. 1).

The decision to proceed with M-PHP was taken after discussion at a multidisciplinary meeting. Patients with known single-site extrahepatic disease were included if the disease was nonprogressive following previous treatments or amenable to ablative treatment. Any number and type of prior treatments were permitted. Approval from University Hospital Southampton research/audit board to perform retrospective data collection and outcome analysis was obtained (No. 6469).

Baseline imaging was obtained within 6 weeks of treatment with staging contrast-enhanced computed tomography (CT) chest/abdomen/pelvis and contrast-enhanced liver MRI to determine vascular anatomy, baseline volume, and distribution of measurable disease; identify extrahepatic disease; and facilitate procedural planning.

Procedural details

Cases were performed under general anaesthetic with continuous monitoring of the central venous and arterial pressure in a dedicated interventional radiology suite. Patients received melphalan at a dose of 3 mg/kg (ideal body weight) delivered using the Hepatic CHEMOSAT Delivery System (Delcath Systems, Inc., New York, USA) with the GEN 2 filter in line with the manufacturer's recommendations, which have been described in detail previously [13].

Patients were monitored for 4 h post procedure in a theatre recovery area before being transferred to a surgical ward. All received pegylated granulocyte colony-stimulating factor (G-CSF) 24–72 h post intervention. Patients were discharged once haematological blood parameters had stabilized and they were clinically well. Post hospital discharge, patients underwent blood tests to monitor liver function and full blood count weekly until recovered. Repeat imaging (CT and MRI) was performed every 6–12 weeks and additional M-PHP sessions were scheduled provided there was no evidence of disease progression, treatment was adequately tolerated, and treatment-related toxicities had resolved. If disease progression was attributable to differential perfusion of liver parenchyma due to anatomic constraints, subsequent attempts with M-PHP were made to preferentially target these areas.

M-PHP procedures were undertaken at approximately 6–10-week intervals with the number of treatments per patient depending upon disease response and tolerability.

Survival definitions and response assessment

OS was calculated as the time from first M-PHP treatment to death from any cause. PFS was defined as the time from first treatment to first radiologically documented progressive disease (PD) or death from any cause, whichever occurred first. For subjects who had not progressed at the data collection cut-off date (1 January 2021), OS and PFS were assigned censored in the analysis.

Tumour and overall response were assessed on CT and MRI imaging as per RECIST 1.1 guidelines. Disease control rate (DCR) was calculated as the proportion of patients with complete response (CR), partial response (PR), or stable disease for at least 9 weeks (SD).

Treatment-related toxicity and serious adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (2017).

Statistical analysis

Median values and SD were used to describe differences between groups. Kaplan–Meier estimations were used to assess the distribution of time to event variables including OS and PFS. The log-rank test was used to compare curves for univariate analysis. Hazard ratios with 95% confidence intervals were used to determine predictors for OS with significant response indicated by $P < 0.05$.

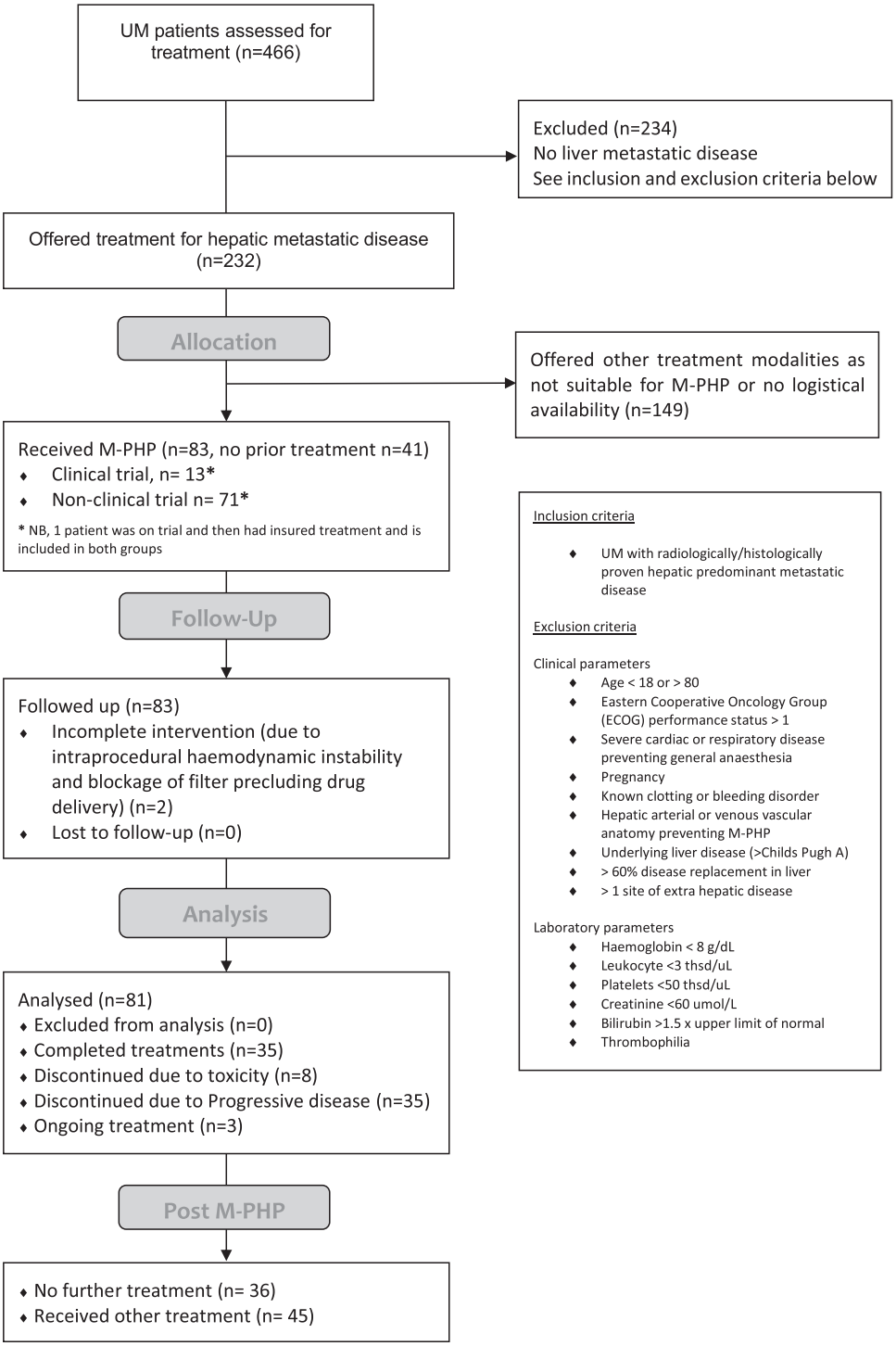
Analyses were performed using MATLAB (R2019b) (The MathWorks Inc., Natick, Massachusetts, USA).

Results

Patient characteristics

In total, 252 treatments with M-PHP were performed in 83 patients (Fig. 1). Two patients each had a single incomplete treatment, one due to intraprocedural haemodynamic instability on inflation of the inferior vena cava

Fig. 1



Consort diagram.

balloon catheter and the other (later confirmed positive for antiphospholipid syndrome) due to blockage of the filter, precluding drug administration in both cases. Hence, both were excluded from response and survival outcome analyses and only included in adverse events analysis.

Baseline characteristics are presented in Table 1. All patients had pathologically/radiologically confirmed hepatic mUM. Sixty-nine (85.2%) patients had intrahepatic disease only at the time of workup for M-PHP whereas 12 (14.8%) patients had both intrahepatic and

small-volume (single organ) extrahepatic disease (six lungs, four bones, one lymph node, and one spleen).

Forty-one (50.6%) patients had received other treatments, either systemic or liver-directed, before M-PHP (Supplementary Materials 2–3, Supplemental digital content 1, *http://links.lww.com/MR/A286*). The median time to treatment from diagnosis of stage IV disease was 158 ± 340 days.

The median number of M-PHP treatments was 3 ± 1.6 (range, 1–8). The median length of stay (LoS) was 3 days across all M-PHP treatments and 4 days for the first M-PHP treatment. Eight (9.9%) patients discontinued therapy due to toxicity, 35 (43.2%) due to disease progression, 35 (43.2%) completed planned treatment, and 3 (3.7%) are continuing treatment.

Following cessation of M-PHP, 36 (44.4%) patients had no further treatment whereas 45 (55.6%) underwent various palliative treatments following PD, the majority being systemic immunotherapy agents (80.6%) (Supplementary Material 3, Supplemental digital content 1, *http://links.lww.com/MR/A286*).

Response analysis

Best overall response was CR in 7/81 (8.6%), PR 42/81 (51.9%), SD 16/81 (19.8%), and PD 16/81 (19.8%); hepatic only CR was 10/81 (12.3%), PR 43/81 (53.1%), SD 19/81 (23.5%), and PD was 9/81 (11.1%) (Table 2). Overall response rate (ORR) was 49/81 (60.5%).

Table 1 Baseline patient characteristics

	N	%
Demographics		
Median age at first M-PHP treatment	59.3 (12.2) years	
Median time to treatment from diagnosis of stage IV disease	158 (340) days	
Sex		
Female	45	55.6
Male	36	44.4
Median number of cycles	3	
<3 cycles	38	46.9
≥3 cycles	43	53.1
Disease extent at treatment onset		
Intrahepatic only	69	85.2
Intrahepatic and extrahepatic	12	14.8
Disease burden		
High disease burden (>10 lesions/>50% volume replacement)	42	51.9
Low disease burden	39	48.1
Potential adverse outcome indicators		
LDH		
Abnormal	16	19.8
Normal	30	37.0
Unknown	35	43.2
Performance status		
1	6	7.4
0	75	92.6
Reason for discontinuation		
Toxicity	8	9.88
Progressive disease	35	43.21
Completed treatments	35	43.21
Ongoing	3	3.70

LDH, lactate dehydrogenase; MPHP, melphalan percutaneous hepatic perfusion.

Overall and hepatic DCR (defined as CR + PR + SD) were 80.2% and 88.9%, respectively.

Survival analysis

Median follow-up was 12.9 months for all patients and 13.9 months for patients still alive and being followed-up. At the cut-off date, 15 (18.5%) patients remained alive with three continuing M-PHP treatments and 66 (81.5%) patients were deceased.

Median OS was 14.9 months from the time of first treatment; 1- and 2-year median OS rates were 62% and 27%, respectively (Fig. 2a).

OS of patients was significantly different ($P < 0.0001$) depending on the best hepatic response: 34.7 months for CR vs. 16.9, 10.5, and 7.7 for PR, SD, and PD, respectively (Fig. 2c).

Predictors of improved overall survival

Univariate analysis identified three predictors of OS. Patients with abnormal baseline lactate dehydrogenase (LDH) had significantly decreased OS of 12.1 vs. 21.5 months [hazard ratio (HR) = 2.45 (1.06–5.64), $P = 0.00386$; Fig. 2d]. Second, high disease burden at onset (>50% hepatic parenchymal replacement or >10 deposits) was associated with a decreased median OS of 10.9 vs. 23.5 months in those with low disease burden [HR = 2.53 (1.52–4.19), $P < 0.0001$] (Fig. 2e). Third, the median number of treatments received per patient was three and patients who received three or more treatments had a significantly better median OS of 20.1 vs. 11.1 months for those who had less than three treatments [HR = 1.76 (1.07–2.89), $P = 0.017$; Supplementary Material 4D, Supplemental digital content 1, *http://links.lww.com/MR/A286*].

OS in patients with no extrahepatic disease at baseline was 15.1 vs. 9.1 months (Fig. 2f) for patients with extrahepatic disease; this difference did not reach statistical significance – $P = 0.126$, HR = 1.64 (0.756–3.56).

There was no statistically significant difference in median OS for patients receiving procedures carried out between 2012 and 2016 vs. 2016 and 2020 (Supplementary Material 4A, Supplemental digital content 1, *http://links.lww.com/MR/A286*) and nor with respect to age, sex, previous or subsequent liver-directed or systemic treatment, prolonged lead time from diagnosis of stage IV disease, or Eastern Cooperative Oncology Group (ECOG) performance status.

Progression-free survival and time to progression

Median PFS was 8.4 months (Fig. 2b) with a 1-year PFS of 30%. In our cohort, there was no significant increase in PFS with the presence of intrahepatic disease only vs. intra- and extrahepatic disease at baseline, reflecting the multidisciplinary team decision to accept patients for M-PHP only with nonprogressive extrahepatic disease or disease that

Table 2 Response rates by RECIST 1.1

	Hepatic		Overall		Median OS by best hepatic response
	N	%	*N*	%	Months
Best overall and hepatic response					
CR	10	12.3	7	8.6	34.7
PR	43	53.1	42	51.9	16.9
SD	19	23.5	16	19.8	10.5
PD	9	11.8	16	19.8	7.7
Total	81		81		
Best hepatic response by disease burden					
	High		Low		
CR/PR	24	57.1%	29	74.4%	
SD	12	28.6%	7	17.9%	
PD	6	14.3%	3	7.7%	
Total	42	100.0%	39	100.0%	
Median OS (months)	10.9		23.5		

High disease burden = at least 10 hepatic metastases or at least 50% hepatic involvement. Low disease burden = less than 10 hepatic metastases or less than 50% hepatic involvement.
CR, complete response; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

could be ablated (P = 0.13; Supplementary Material 4B, Supplemental digital content 1, *http://links.lww.com/MR/A286*). The median time to progression was 10.8 months.

Safety analysis

M-PHP therapy was generally well tolerated with no treatment-related fatalities or 90-day treatment-related mortality. One patient (1.2%) died of disease progression on Day 88. The mean and median LoS were 3.65 and 3 days across all M-PHP treatments (range, 2–8).

According to CTCAE v5 grading criteria, in total, 43 grade 3 (29) or 4 (14) treatment-related adverse events (TRAE) occurred across 23 (27.7%) patients during therapy (Table 3). There was no grade 5 TRAE. There were statistically fewer grade 3 or 4 complications per patient during 2016–2020 vs. 2012–2016 (0.17 vs. 0.90 per patient, $P < 0.001$) and a trend towards fewer total complications per patient over the same period (2.15 vs. 2.83, $P = 0.17$).

Fifteen (18.1%) patients experienced intraprocedural complications including filter blockage (6/83) 7.2%, coagulopathy (3/83) 3.6%, prolonged hypotension (3/83) 3.6% and circuit leak (1/83) 1.2%. Two (2.4%) patients suffered intraprocedural complications precluding melphalan administration. Five (6%) patients had a 20% melphalan dose reduction for subsequent treatments due to toxicity, interval abnormal liver function tests, and filter blockage.

The most common haematological toxicity was anaemia, recorded in 45.6% (38/83) and grades 3–4 in 13.3% (11/83). Thrombocytopaenia was seen in 42.2% (35/83) of patients, occurring at grades 3–4 in 12% (10/83). Overall, 31.3% (26/83) required platelet transfusion and 19.3% (16/83) required red cell transfusion beyond the standard intraprocedure blood product replacement protocol. Additionally, neutropenia developed in 20.5% (17/83), with 6% (5/83) developing neutropenic sepsis.

Nonhaematological complications are listed in Table 3 and were predominantly of low grade.

Discussion

In the absence of established standards of care, there is an urgent need to provide effective treatment for mUM. Historically, up to 50% of mUM patients died due to uncontrolled intrahepatic disease before extrahepatic deposits could be detected [7]. M-PHP achieves 10-fold higher peak perfusate drug concentrations than systemic administration by isolating the hepatic circulation [11], overcoming UM resistance to conventional cytotoxic agents and thus establishing at least temporary hepatic disease control.

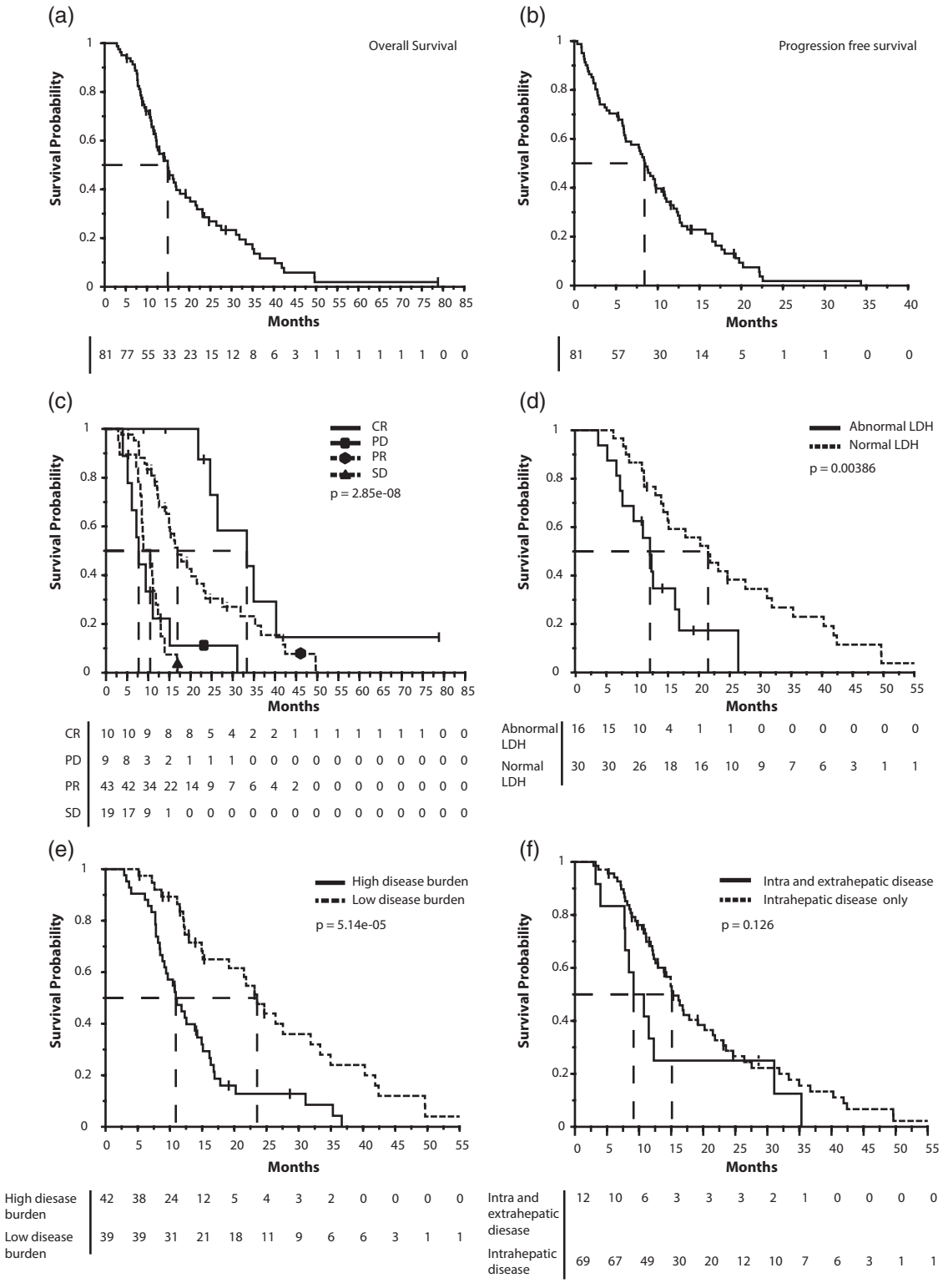
Melphalan percutaneous hepatic perfusion outcomes

M-PHP remains a procedure with a limited number of published studies demonstrating patient outcomes; those that exist are limited by their retrospective nature, small patient numbers, and significant variability in results. Meta-analyses and systematic reviews [14–17] repeatedly cite variability of patient selection and study design as the main basis for differences in OS across both systemic and liver-directed mUM treatments. This is evident in the M-PHP literature with median OS spread from 9.6 to 27.4 months (Table 4). However, as sample sizes increase, a trend is emerging in PFS and OS and our study – the largest yet – confirms this.

Here, we report a median OS of 14.9 months and 1- and 2-year OS of 62% and 27%, respectively with an overall PFS of 8.4 months. This correlates well with previous M-PHP studies and compares favourably to all reported results of systemic therapies to date. Relative comparison with alternative liver-directed therapies is difficult as studies often focus on OS alone.

Importantly, high best hepatic response rates (CR 12.3% and PR 53.1%) were clinically meaningful with best OS

Fig. 2



(a) Overall survival; (b) progression-free survival; (c–f) OS stratified according to (c) best hepatic response, (d) LDH, (e) disease burden, and (f) baseline intrahepatic or intrahepatic and extrahepatic disease. Each time interval is noted under the Kaplan–Meier curve. LDH, lactate dehydrogenase; OS, overall survival.

Table 3 Complications

	Any grade		Grades 3–4	
	Number of patients	%	Number of patients	%
Treatment-related adverse events				
Adverse event				
Intraprocedural complications				
Filter blockage event	6	7.2	1	1.2
Coagulopathy with bleeding sequalae	3	3.6	0	0.0
Prolonged hypotension	3	3.6	1	1.2
Circuit leak/failure	1	1.2	0	0.0
Vascular access failure	0	0.0	0	0.0
Postprocedure complications				
Haematological				
Anaemia	38	45.7	11	13.3
RBC transfusion	16	19.3		
Thrombocytopenia (post ICU stay)	35	42.2	10	12.0
Platelet transfusion	26	31.3		
Neutropenia	17	20.5	11	13.3
Neutropenic sepsis	5	6.0		
Nonhaematological				
Fatigue	31	37.3	1	1.2
Epigastric pain	15	18.1	0	0.0
Nausea	13	15.7	0	0.0
Posttreatment bleeding complication	7	8.4	0	0.0
Venous thromboembolism (PE/DVT within 2 months)	5	6.0	0	0.0
Vomiting	4	4.8	0	0.0
Arrhythmias	3	3.6	2	2.4
Alopecia	3	3.6	1	1.2
Cardiac ischaemia	3	3.6	0	0.0
Mucositis	2	2.4	0	0.0
Diarrhoea	1	1.2	1	1.2
Cerebrovascular event	1	1.2	0	0.0
Other	35	42.2	6	7.2

DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; RBC, red blood cell.

Table 4 Outcomes of cohort studies of melphalan percutaneous hepatic perfusion in the treatment of metastatic uveal melanoma ordered by sample population size followed by outcomes of trials of selected systemic therapies

Agent	Mechanism	No. of patients	ORR	Median PFS (months)	Median OS (months)	CTCAE grade ≥3
Melphalan [18]	Chemosaturation	16	60%	11.1	27.4	43.8%
Melphalan [19]	Chemosaturation	18	54%	12.4	9.6	Unknown
Melphalan [20]	Chemosaturation	30	42.3%	6.0	12.0	Unknown
Melphalan [21]	Chemosaturation	35	72%	7.6	19.1	Unknown
Melphalan [22]	Chemosaturation	51	47%	8.1	15.3	Unknown
Cabozantinib [23]	MEK/VEGF inhibitor	23	5%	3.8	9.4	32%
Ipilimumab [24]	Anti-CTLA-4	82	5%	3.6	6.0	10%
Nivolumab + ipilimumab [25]	Anti-PD-1 and anti-CTLA-4	52	11.5%	3.0	12.7	57.7%
Pembrolizumab [9]	Anti-PD-1	25	8%	3.0	Not reached	20%
Selumetinib [26]	MEK1/2 inhibitor	101	14%	3.7	11.8	37%
Tebentafusp [10]	ImmTAC	127	5%	2.8	16.8	30%
Trametinib ± Akt inhibitor [27]	MEK1/2 inhibitor	40	5%	3.6	Not reached	Unknown

CTCAE grade has been provided on a per-patient basis; however, previous M-PHP studies have predominantly provided this on a per-procedure rather than per-patient basis.

CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ImmTAC, immune mobilizing monoclonal T-cell receptors against cancer; MEK, mitogen-activated protein kinase; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

outcomes seen in patients with CR and PR at 33.4 and 16.9 months, respectively, vs. 10.5 and 7.7 months for SD and PD. Additionally, previous studies have demonstrated no reduction in quality of life over the course of M-PHP treatment [18,20].

In our data, M-PHP provided hepatic disease control in 88.9% of cases with an ORR of 60.5%, far exceeding response rates seen in systemic therapies and consistent with those observed in previous M-PHP cohort studies.

Factors influencing OS to a statistically significant degree included baseline LDH (abnormal 12.1 months vs. normal 21.5 months, $P = 0.00386$) and disease burden (high 10.9 months vs. low 23.5 months, $P < 0.0001$). Median OS was not significantly lower in the small subpopulation with intrahepatic and single-site extrahepatic disease ($n = 12$) vs. those with intrahepatic disease only (9.1 vs. 15.1 months, $P = 0.126$). Hence, this may be a reasonable group to treat for now until further data becomes available. Patient numbers were insufficient to determine any

statistically significant survival difference for those with particular sites of extrahepatic disease.

Patients receiving more M-PHP treatments survived longer (20.2 months for three or more treatments vs. 11.1 months if treatments range between one and two, $P = 0.017$); however, this is difficult to interpret: although the aim was for all patients to receive at least two M-PHP sessions, additional treatments were in some cases limited by logistical considerations. Conversely, patients failing to respond after two technically adequate sessions would not be offered further cycles and may represent a group with worse outcomes.

In this cohort, 23 (27.7%) patients developed a grade 3 or 4 TRAE across their treatment cycles (median = three treatments), most frequently haematological. This is lower than that reported by Artzner *et al.* [18] (7/16, 43.8%) and a statistically significant reduction in grade 3 and 4 complications was demonstrated between 2016 and 2020 vs. 2012 and 2016, indicating improvement and a potential learning curve with the number of cases performed. Reassuringly, no treatment-related mortality was seen in 252 treatments and there was only one (1.2%) 90-day mortality due to disease progression. Despite the complexity of treatment, the median LoS was short at 3 days.

Melphalan percutaneous hepatic perfusion compared to alternatives in metastatic uveal melanoma

A significant limitation comparing M-PHP to other mUM treatment modalities is that it requires patient selection (Fig. 1) and is restricted to a group of haemodynamically fit patients with sufficient hepatic reserve and ECOG performance status without significant extrahepatic disease.

Nevertheless, all our patients had uncontrolled baseline intrahepatic disease with over 50% having a high disease burden in the liver and would be expected to respond poorly to non-liver-directed therapies [9,25].

Our study is limited in its lack of any control or alternative treatment arm, and the confounding effects of treatments received by patients both pre and post M-PHP (Supplementary Materials 2–3, Supplemental digital content 1, *http://links.lww.com/MR/A286*) – although with no statistically significant effect on median OS.

Early prognosis in mUM is driven by hepatic disease burden which forms the rationale behind liver screening post primary treatment in high-risk UM. Multiple studies have suggested immunotherapies trialled to date are less effective in patients with uncontrolled hepatic only disease [9,25] and M-PHP appears to offer superior tumour response and PFS compared to them.

On the contrary, the shape of the OS survival curve post M-PHP does not reveal a plateau in contrast with immunotherapy in similar indications – including CM – indicating that the underlying tumour biology is unchanged. The emerging effect of M-PHP on the natural history of mUM is in keeping with its primary mode and site of action: significant early/medium-term benefit by intrahepatic disease control due to direct cytotoxicity but without sufficient immune-mediated effects that could establish long-term immune and extrahepatic disease control.

Although our current data show M-PHP offers superior early outcomes to the standard of care immunotherapy, we note that advanced genetic profiling of mUM tumour deposits demonstrates IDO1 and TIGIT to be the most highly expressed immune checkpoint inhibitors, suggesting that immune targeting to date may have been suboptimal [28].

Areas for further investigation

The landscape of treatment options for patients with mUM is blighted by lack of standardization in patient selection, study design, and few multi-arm trials – problems exacerbated by the absence of evidence-based standard of care.

Although multi-arm trials of the surgical correlate IHP are underway [29], the largest international multicentre trial to date in M-PHP, originally designed to compare this with the standard of care options, has become a single-arm trial of M-PHP, mostly due to difficulty in retaining patients allocated to non-M-PHP treatment arms [30].

Further investigation is warranted to clarify the optimal sequencing and timing of treatment modalities: immunotherapy outcomes are poor in patients with uncontrolled liver disease whereas M-PHP has the most promising hepatic disease response rates of any nonsurgical therapy so far. A multimodality approach combining both treatment strategies might be able to offer both immediate control of liver disease together with durable responses associated with checkpoint inhibitors in other settings.

PHP is a technique for which the active agent can be altered, providing flexibility if alternative drugs to melphalan are found to have better efficacy. Moreover, chemical modifications of melphalan have been applied to haematological malignancies in vitro with improvements in toxicity [31] and a similar approach could be considered for mUM and trialled if promising.

With expanding systemic options emerging, tebentafusp, together with other immune checkpoint inhibitors such as anti-TIGIT, may also enter the treatment landscape in the next few years. The declining side effect profile we have demonstrated with experience of M-PHP suggests it may be appropriate to trial a combination strategy of M-PHP together with immunotherapy.

Conclusion

This study, as the largest to date, adds to the mounting body of evidence supporting the use of M-PHP in liver

only or liver predominant metastatic disease, becoming safer with experience and offering excellent short- and medium-term hepatic disease control and some limited long-term benefit. Combination therapy of M-PHP and immunotherapy may represent a viable path to surpassing the limited improvements in OS observed across all treatment modalities to date.

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Conflicts of interest

Sachin Modi: Consultancy contract with Delcath, received honorarium for lectures and proctoring. Sanjay Gupta: Consultancy contract with Delcath, received honorarium for lectures and proctoring. Brian Stedman: Consultancy contract with Delcath, received honorarium for lectures. For the remaining authors, there are no conflicts of interest.

References

1 Vidwans SJ, Flaherty KT, Fisher DE, Tenenbaum JM, Travers MD, Shrager J. A melanoma molecular disease model. *PLoS One* 2011; **6**:e18257.

2 Amaro A, Gangemi R, Piaggio F, Angelini G, Barisione G, Ferrini S, Pfeffer U. The biology of uveal melanoma. *Cancer Metastasis Rev* 2017; **36**:109–140.

3 Karlsson J, Nilsson LM, Mitra S, Alsén S, Shelke GV, Sah VR, *et al*. Molecular profiling of driver events in metastatic uveal melanoma. *Nat Commun* 2020; **11**:1894.

4 Field MG, Durante MA, Anbunathan H, Cai LZ, Decatur CL, Bowcock AM, *et al*. Punctuated evolution of canonical genomic aberrations in uveal melanoma. *Nat Commun* 2018; **9**:116.

5 Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology* 2011; **118**:1881–1885.

6 Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, *et al*. Collaborative Ocular Melanoma Study Group, development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No. 26. *Arch Ophthalmol* 2005; **123**:1639–1643.

7 Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci* 2003; **44**:4651–4659.

8 Gragoudas ES, Egan KM, Seddon JM, Glynn RJ, Walsh SM, Finn SM, *et al*. Survival of patients with metastases from uveal melanoma. *Ophthalmology* 1991; **98**:383–389.

9 Karydis I, Chan PY, Wheater M, Arriola E, Szlosarek PW, Ottensmeier CH. Clinical activity and safety of pembrolizumab in ipilimumab pre-treated patients with uveal melanoma. *Oncoimmunology* 2016; **5**:e1143997.

10 Sacco JJ, Carvajal R, Butler MO, Shoushtari AN, Hassel JC, Ikeguchi A, *et al*. A phase II, multi-center study of the safety and efficacy of tebentafusp (IMCgp100) in patients with metastatic uveal melanoma. *Ann Oncol* 2020; **31**(Suppl 7):S1442–S1443.

11 Pingpank JF, Libutti SK, Chang R, Wood BJ, Neeman Z, Kam AW, *et al*. Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. *J Clin Oncol* 2005; **23**:3465–3474.

12 Hughes MS, Zager J, Faries M, Alexander HR, Royal RE, Wood B, *et al*. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. *Ann Surg Oncol* 2016; **23**:1309–1319.

13 Meijer TS, Burgmans MC, Fiocco M, de Geus-Oei LF, Kapiteijn E, de Leede EM, *et al*. Safety of percutaneous hepatic perfusion with melphalan in patients with unresectable liver metastases from ocular melanoma using the Delcath systems' second-generation hemofiltration system: a prospective non-randomized phase II trial. *Cardiovasc Intervent Radiol* 2019; **42**:841–852.

14 Rantala ES, Hernberg MK, Tero T. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res* 2019; **29**:561–568.

15 Khoja L, Atenafu EG, Suciu S, Leyvraz S, Sato T, Marshall E, *et al*. Meta-analysis in metastatic uveal melanoma to determine progression-free and overall survival benchmarks: an International Rare Cancers Initiative (IRCI) ocular melanoma study. *Ann Oncol* 2019; **30**:1370–1380.

16 Rodriguez-Vidal C, Fernandez-Diaz D, Fernandez-Marta B, Lago-Baameiro N, Pardo M, Silva P, *et al*. Treatment of metastatic uveal melanoma: systematic review. *Cancers (Basel)* 2020; **12**:2557.

17 Rowcroft A, Loveday BPT, Thomson BNJ, Banting S, Knowles B. Systematic review of liver directed therapy for uveal melanoma hepatic metastases. *HPB (Oxford)* 2020; **22**:497–505.

18 Artzner C, Mossakowski O, Hefferman G, Grosse U, Hoffmann R, Forschner A, *et al*. Chemosaturation with percutaneous hepatic perfusion of melphalan for liver-dominant metastatic uveal melanoma: a single center experience. *Cancer Imaging* 2019; **19**:31.

19 Vogl TJ, Koch SA, Lotz G, Gebauer B, Willinek W, Engelke C, *et al*. Percutaneous isolated hepatic perfusion as a treatment for isolated hepatic metastases of uveal melanoma: patient outcome and safety in a multi-centre study. *Cardiovasc Intervent Radiol* 2017; **31**:31.

20 Schönfeld L, Hinrichs JB, Marquardt S, Voigtländer T, Dewald C, Koppert W, *et al*. Chemosaturation with percutaneous hepatic perfusion is effective in patients with ocular melanoma and cholangiocarcinoma. *J Cancer Res Clin Oncol* 2020; **146**:3003–3012.

21 Meijer TS, Burgmans MC, de Leede EM, de Geus-Oei LF, Boekestijn B, Handgraaf HJM, *et al*. Percutaneous hepatic perfusion with melphalan in patients with unresectable ocular melanoma metastases confined to the liver: a prospective phase II study. *Ann Surg Oncol* 2021; **28**:1130–1141.

22 Karydis I, Gangi A, Wheater MJ, Choi J, Wilson I, Thomas K, *et al*. Percutaneous hepatic perfusion with melphalan in uveal melanoma: a safe and effective treatment modality in an orphan disease. *J Surg Oncol* 2018; **117**:1170–1178.

23 Daud A, Kluger HM, Kurzrock R, Schimmoller F, Weitzman AL, Samuel TA, *et al*. Phase II randomised discontinuation trial of the MET/VEGF receptor inhibitor cabozantinib in metastatic melanoma. *Br J Cancer* 2017; **116**:432–440.

24 Maio M, Danielli R, Chiarion-Sileni V, Pigozzo J, Parmiani G, Ridolfi R, *et al*. Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. *Ann Oncol* 2013; **24**:2911–2915.

25 Piulats JM, Espinosa E, de la Cruz Merino L, Varela M, Alonso Carrión L, Martín-Algarra S, *et al*. Nivolumab plus ipilimumab for treatment-naïve metastatic uveal melanoma: an open-label, multicenter, phase II trial by the Spanish multidisciplinary melanoma group (GEM-1402). *J Clin Oncol* 2021; **39**:586–598.

26 Carvajal RD, Sosman JA, Quevedo JF, Milhem MM, Joshua AM, Kudchadkar RR, *et al*. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *JAMA* 2014; **311**:2397–2405.

27 Shoushtari AN, Kudchadkar RR, Panageas K, Murthy RK, Jung M, Shah R, *et al*. A randomized phase 2 study of trametinib with or without GSK2141795 in patients with advanced uveal melanoma. *J Clin Oncol* 2016; **34**(Suppl 15):9511.

28 Robertson AG, Shih J, Yau C, Gibb EA, Oba J, Mungall KL, *et al*.; TCGA Research Network. Integrative analysis identifies four molecular and clinical subsets in uveal melanoma. *Cancer Cell* 2017; **32**:204–220.e15.

29 Olofsson R, Ny L, Eilard MS, Rizell M, Cahlin C, Stierner U, *et al*. Isolated hepatic perfusion as a treatment for uveal melanoma liver metastases (the SCANDIUM trial): study protocol for a randomized controlled trial. *Trials* 2014; **15**:317.

30 Percutaneous Hepatic Perfusion in Patients With Hepatic-dominant Ocular Melanoma (FOCUS); NCT02678572; Multi-centre, single-arm, open-label study; US and Europe. https://clinicaltrials.gov/ct2/show/NCT02678572

31 Gajek A, Poczta A, Łukawska M, Cecuda-Adamczewska V, Tobiasz J, Marczak A. Chemical modification of melphalan as a key to improving treatment of haematological malignancies. *Sci Rep* 2020; **10**:4479.