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REVIEW ARTICLE

Salvage treatment for testicular cancer with standard- or high-dose chemotherapy: a systematic review of 59 studies

Fausto Petrelli[1] · **Andrea Coinu**[2] · **Giovanni Rosti**[3] · **Paolo Pedrazzoli**[3] · **Sandro Barni**[1]

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Abstract Relapsed germ cell tumor (GCT) is a highly curable cancer with standard-dose platinum-based chemotherapy (CT); however, high-dose CT (HDCT) is seldom used as salvage therapy instead or after conventional CT. We conducted a systematic review of published trials to compare outcomes between standard-dose CT and HDCT in patients with relapsed GCT after first-line therapy for advanced disease. A literature search was carried out in multiple electronic databases (PubMed, Embase, Scopus, Web of Science, and The Cochrane Library), and studies reporting salvage treatment of relapsed GCT with standard-dose or carboplatin–etoposide-based HDCT were selected. Overall response rate, median overall survival (OS), and the 1-, 2-, 3-, and 5-year OS rates were pooled, and the significance of difference between arms was assessed with a Chi-square test. Twenty-nine standard-dose and 31 HD studies were included in the meta-analysis. For standard-dose CT versus HDCT, there was no significant difference in median OS (14.8 months and 24.09 months, respectively; $P = 0.09$) or in 1-, 2-, 3-, or 5-year survival rate (standard-dose CT, 64.2, 63.6, 45.1, and 43%, respectively; HDCT, 63.7, 51.2, 46.7, and 45%, respectively; $P = 0.9$, $P = 0.4$, $P = 0.75$, and $P = 0.06$). Conventional dose regimens and HDCT were associated with comparable efficacy when used as salvage therapies in relapsed GCTs as second-line therapy or beyond. However, the selection of ideal candidates for more or less intensive treatments deserves further research in the near future.

Keywords Testicular cancer · Second line · Chemotherapy · High dose · Review

Introduction

Testicular germ cell tumors (GCTs) are highly curable, and even those in the metastatic stage at diagnosis are associated with high overall survival (OS) rates with standard platinum-based chemotherapy (CT). Usually, three or four cycles of bleomycin–etoposide–cisplatin (BEP)-based CT are prescribed as first-line therapy according to risk group, and these lead to a high cure rate in advanced disease [1, 2]. Recurrence in patients with metastatic disease is generally in the first two years from diagnosis. The probability of surviving and remaining disease free increases substantially in those with a favorable initial response to treatment. While the majority of subjects with metastatic GCTs are cured with first-line CT, the prognosis of metastatic patients with recurrence after first-line CT still seems unsatisfactory. Even if men who are diagnosed with relapsed or refractory testicular GCTs should offered the opportunity to enroll in clinical studies, combination platinum-based CT containing other active agents, such as ifosfamide and vinblastine or taxanes (VIP or TIP regimens), is usually offered [3–5]. Due to the chemosensitivity of testicular cancer, another second-line option is high-dose CT (HDCT) plus autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation (PBSCT or ABMT). The heterogeneous data reported in the literature are related to different

✉ Fausto Petrelli
faupe@libero.it

[1] Oncology Unit, Oncology Department, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047 Treviglio, BG, Italy

[2] Oncology Unit, Giovanni Paolo II Hospital, Olbia, OT, Italy

[3] Division of Medical Oncology, Department of Hemato-Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

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populations included according to histology, primary site, and response to prior CT. In historical retrospective studies or prospective case series, a similar or even better outcome has been reported with HDCT as the first salvage therapy when compared with standard-dose CT, at least in patients with a poorer prognosis [6, 7].

Due to the paucity of data from large randomized trials about which is the best approach in relapsed/refractory patients with GCTs, we have performed a systematic review of published trials to compare the efficacy of standard-dose CT and HDCT in advanced GCT after failure of at least one line of standard treatment for advanced disease.

Methods

A systematic search of the literature of electronic databases (PubMed, Embase, Scopus, Web of Science, and The Cochrane Library) for all published studies without date restrictions was conducted using the terms ("testicular cancer" [All Fields] OR "germ cell" [All Fields]) AND (("cisplatin" [MeSH Terms] OR "cisplatin" [All Fields]) OR ("etoposide" [MeSH Terms] OR "etoposide" [All Fields]) OR ("vinblastine" [MeSH Terms] OR "vinblastine" [All Fields]) OR ("paclitaxel" [MeSH Terms] OR "paclitaxel" [All Fields]) OR ("ifosfamide" [MeSH Terms] OR "ifosfamide" [All Fields]) OR "high dose" [All Fields]) AND (refractory [All Fields] OR ("recurrence" [MeSH Terms] OR "recurrence" [All Fields] OR "relapse" [All Fields]) OR recurrent [All Fields] OR resistant [All Fields] OR "second line" [All Fields]).

Study eligibility

The studies were independently reviewed by two authors (FP and AC) for eligibility. Patients enrolled must have had a diagnosis of refractory (progressing during or within 1 month after completion of previous CT) or relapsed GCT after at least one line of conventional platinum-based CT (usually BEP). Trials had to include adult patients with mainly gonadal GCT; extragonadal primary sites were permitted provided they represented less than 50% of the total study. Trials using salvage standard-dose polychemotherapy and HDCT including carboplatin (CBDCA) and etoposide (VP-16), with peripheral blood stem cell (PBSC) transplantation or autologous bone marrow transplantation (ABMT) were included in this analysis. Phase 1 trials, single-agent studies, and trials that enrolled fewer than 20 patients were excluded from the analysis. Other therapeutics or experimental agents were not allowed for inclusion. Only studies published in full form were considered. If data had been presented multiple times, the most updated version was used, and the older data were excluded. Studies were included if at least one of the outcome measures was extractable from the paper. Quality assessment of the included studies was performed using the Newcastle–Ottawa Scale for observational or retrospective studies and the Jadad score for randomized studies.

Data extraction and statistical analysis

The extracted data included the type of study, number of patients, line of treatment, treatment schedule, and clinical outcomes, including overall response rate (ORR), median OS, 1-, 2,- 3-, and 5-year OS. From trials that investigated multiple treatment arms, data were only included from the arms that used standard CT or HDCT. The outcome data extracted for each arm were analyzed using random effects models and were reported as weighted measures. Overall treatment-related mortality was extracted for descriptive analysis between the two groups. The comparisons between the two arms were conducted based on weighted estimates. The response rates and 1-, 2-, 3-, and 5-year survival rates reported in the individual studies were pooled, and the significance of difference between standard-dose CT and HDCT was assessed with a Chi-square. Second-line studies were also analyzed separately for median OS and 1-, 2-, and 3-year OS. Those studies included at least 70% of subjects treated with second-line chemotherapy. Heterogeneity among studies was assessed using the Chi-square test. All analyses were performed using Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat) and NCSS 11 statistical software (NCSS, LLC).

Results

Study characteristics

In the initial search of the literature for studies using a standard-dose CT or HDCT as salvage therapy for relapsed or refractory GCT, 2226 studies were retrieved, with 136 studies selected for full-text review. Of these, 59 studies were deemed appropriate and were included in the final analysis ($n = 29$ standard-dose and $n = 31$ HDCT publications). One randomized trial was considered suitable for both analyses. The consort diagram is shown in Fig. 1, and the study characteristics are given in Tables 1 and 2 [3–6, 8–64].

There was only one randomized study comparing standard-dose CT with HDCT. In the standard-dose series, there were 20 prospective or phase 2 studies, and 10 were retrospective series. The number of patients ranged from 21 to 189. The most frequent histology was mixed/non-seminoma (range 0–100%; median 90%) compared to

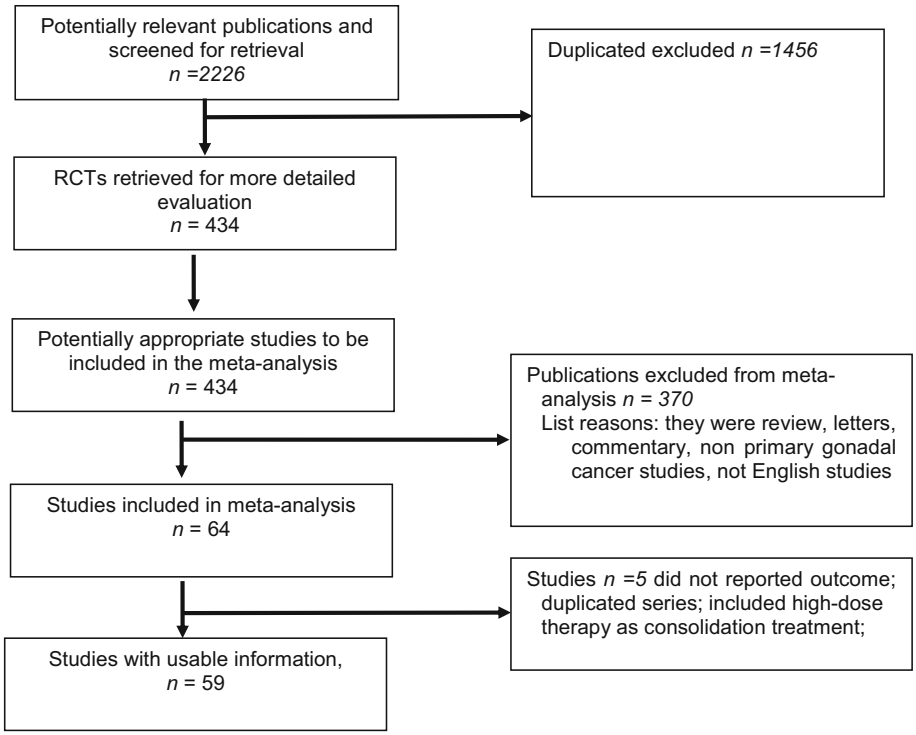

Fig. 1 Overview of trials search and selection

seminoma (range 0–100%; median 9%). Fifteen studies consisted of true second-line therapy (only one previous line of therapy for advanced stage in 100% of patients). The remaining 15 studies included more pretreated patients (at least two prior regimens in 14–100% of subjects). Chemotherapies used were various: gemcitabine-based ($n = 10$), ifosfamide-based ($n = 15$), and other cisplatin-based regimens ($n = 5$). The rate of primary testicular cancer ranged from 64 to 100% of studies (only four did not report these data). Refractory patients ranged from 0 to 100% in standard-dose CT (median 25.4%).

In the high-dose arm, 3 were randomized trials, 16 were prospective series of phases I and II studies, and 12 were retrospective studies. The number of patients ranged from 20 to 341. The most frequent histology was mixed/non-seminoma (range 0–96%; median 85%). Only four publications included true second-line therapy (100% of patients treated in these series). The remaining studies included a population treated in second-line or beyond settings (median of patients enrolled in second-line therapy, 49%). Overall, in 13 studies, HDCT was performed without induction with standard-dose CT; in the remaining studies, at least one cycle of conventional dose therapy was provided. In all studies, HDCT consisted of CBDCA + VP-16-based CT with ABMT or PBSCT. Refractory patients ranged from 0 to 74% in HDCT studies (median 21.7%) and were not significantly different from standard-dose CT cohort (Chi-square for difference, $P = 0.32$).

Standard-dose CT studies included 1781 patients; HDCT studies included 2447 patients.

Overall response rate

Overall, 28 standard-dose CT studies and 24 HDCT studies had data available for ORR evaluation. They were associated with a pooled mean ORR of 51.65 (95% CI 44.7–58.5%) and 62.4% (95% CI 55.7–69%), respectively. The difference in ORR was significant in favor of HDCT (Chi-square for difference, $P = 0.026$) (Table 3).

Median OS

In studies with available data, the survival analysis revealed that standard-dose CT (17 studies) was associated with a pooled mean OS of 14.8 months (95% CI: 8.6–21) compared to 24.09 months for HDCT (20 studies) (T test for difference, $P = 0.09$).

1-, 2-, 3-, and 5-year OS

In standard-dose CT studies, the 1-, 2-, and 3-year OS rates were 64.2, 63.6, and 45.1%, respectively, compared to 63.7, 51.2, and 46.7% in HDCT studies (Chi-square for difference, $P = 0.9, 0.4$, and 0.75, respectively). Also, the 5-year OS did not differ among trials (43 vs. 45%; $P = 0.6$) (Fig. 2).

Treatment-related deaths

The pooled mean mortality with standard-dose CT and HDCT was 1.29 and 6.46%, respectively (Chi-square for difference, $P < 0.001$) in 27 and 31 studies.

Table 1 Characteristics of studies using standard-dose chemotherapy

Author/year	Type of study/ quality score (NOS)	N[b] pts/ primary testicular site (%)	Histology % (S vs NS/ mixed)	Second line (%)	≥3rd (%)	Refractory/ HDCT (%)	Schedule	ORR (%)	Toxic deaths (%)	Median OS (months)	1y OS (%)	2y OS (%)	3y/5y OS (%)
Bedano/ 2006	Phase 2/6	30/83	–	Median 2 previous line	–	100/13.3	EPI + CDDP	57	0	14.5	60	23	17/–
Fizazi/2014	Phase 2/7	37/97	26 versus 74	100	0	0/0	GEM + IFO + CDDP	78	5.4	Not reached	82	73	73/70
Hinton/2002	Phase 2/6	28/64	–	25	75	36/36	GEM + PAC	21.4	0	8.3	–	–	–/–
Kondagunta/ 2005	Phase 2/8	46/100	11 versus 89	100	0	0/4	PAC + IFO + CDDP	63	2.1	Not reached	85	78	75/75
Lohrer/1998	Prospective/8	135/73	8 versus 92	100	0	0/0	Vinblastine + IFO + CDDP	49.6[a]	2.2	16	56	38	34/34
Mead/2005	Phase 2/7	43/86	20.9 versus 76.7	100	0	9[b]/0	PAC + IFO + CDDP	60[c]	2.3	25	70	54	50/–
Miller/1997	Retrospective/ 7	24/75	100 versus 0	100	0	–/0	Vinblastine + IFO + CDDP	87.5[c]	4.1	Not reached	100	66	62/57
Motzer/2000	Prospective/8	30/100	10 versus 90	100	0	0/0	PAC + IFO + CDDP	80	0	Not reached	90	85	80/80
Necchi/2014	Prospective/8	75/89.3	17.3 versus 82.7	0	100	56/13.3	GEM + PAC + CDDP	49.3	0	13	53	29.5	28/25
Oechsle/ 2011	Phase 2 ($n = 2$)/8	76/82	3 versus 97	0	100	49/83	GEM + PAC + OXA × 8 or GEM + OXA	34	1.3	8	–	–	–/–
Pectasides/ 2004	Phase 2/7	28/93	0 versus 100	3	97	100/14	GEM + OXA	32	0	8.7	–	–	–/–
Pico/2005	Phase 3/4 (Jadad)	128/82	9 versus 91	100	0	0/0	CDDP + VP16 + IFO or vinblastine + IFO + CDDP	67 ($n = 99$)	3	40	70	58	52/50
Seidel/2016	Retrospective/ 7	63/–	10 versus 90	6	94	100/76	GEM + PAC + OXA	44[f]	0	13.3	56	28	28/–
Theodore/ 2008	Phase 2/6	27/74	7 versus 93	7	93	59/18.5	PAC + OXA	3.7	0	8.8	–	–	–/–
Berger/2014	Retrospective/ 7	48/83	19 versus 71	100	0	–/0	CDDP + VP16 + IFO or PAC + IFO + CDDP (77%), other 23%	58	2	59	82	65	62/8
Farhat/1996	Retrospective/ 6	54/83	18 versus 80	81	19	39/–	CDDP + VP16 + IFO or vinblastine + IFO + CDDP	63[d]	0	–	–	–	–/–
Fossa/1999	Retrospective/ 7	164/83	0 versus 100	100	0	–/0	CDDP based	–	–	12	–	–	–/–
Badreldin/ 2015	Retrospective/ 6	72/72	12 versus 88	40	60	13.8/44	PAC + OXA + CPT11	55[p]	6.9	–	–	–	33.4/–

Table 1 continued

Author/year	Type of study/ quality score (NOS)	N[b] pts/ primary testicular site (%)	Histology % (S vs NS/ mixed)	Second line (%)	≥3rd (%)	Refractory/ HDCT (%)	Schedule	ORR (%)	Toxic deaths (%)	Median OS (months)	1y OS (%)	2y OS (%)	3y/5y OS (%)
Hainsworth/ 1985	Prospective/7	51/72.5	9 versus 95	100	0	100/0	CDDP + VP16-based	71[e]	1.9	Not reached	80	70	70/–
Harstrick/ 1991	Prospective/7	30/–	3 versus 97	86	14	36/–	CDDP + VP16 + IFO	33[n]	0	11	40	30	20/–
Loehrer/ 1988	Phase 2/7	56/82	5 versus 95	0	100	0/–	CDDP + VP16 + IFO or vinblastine + IFO + CDDP	36[g]	1.8	12.7	50	40	40/–
McCaffrey/ 1997	Retrospective/ 7	56/82	20 versus 80	100	0	0/0	CDDP + VP16 + IFO or vinblastine + IFO + CDDP	36[h]	0	18	50	45	40/38
Motzer/1991	Retrospective/ 7	94/85	9 versus 91	100	0	0/0	VBAB-6[i], vinblastine + IFO + CDDP, CDDP + VP16 or other regimens	23.4 (CR)	–	8	42	21	20/18
Einhorn/ 2007	Phase 2/7	32/–	–	0	100	–/100	GEM + PAC	31	0	8	25	25	25/25
Necchi/2013	Retrospective/ 8	189/87.8	–	100	0	14.8/	CDDP + VP16 + IFO	53.9	0	21.7	66	52	48/44
Pizzocaro/ 1985	Prospective/5	32/–	19 versus 81	100	0	–/0	CDDP + VP16	65.5[j]	0	–	–	–	–/–
Shamash/ 1999	Prospective/5	65/95	10 versus 80	100	0	–/0	m-BOP[k]	45[l]	2	–	–	–	–/–
Ghosn/1988	Phase 2/5	21/90	0 versus 100	71	29	100/0	CDDP + VP16 + IFO	42[m] ($n = 19$)	0	–	–	–	–/–
Pont/1997	Retrospective/ 6	47[o]/74	0 versus 100	0	100	–/199	CDDP + IFO, CDDP + VP16, CDDP + VP16 + IFO or PAC + IFO ± CDDP	73.5	0	6.5	–	–	–/–

ABMT autologous bone marrow transplantation, *PBSCT* peripheral blood stem cell transplantation, *CR* complete response only

[a] 18% after surgery of residual mass; [b] relapse within 2 months after end of first-line chemotherapy; [c] including 1 patient after surgery of residual mass; [d] 7% after surgery of residual mass; [e] 25% after surgery; [f] 13% after surgery; [g] 9% after surgery; [h] 5% after surgery of residual mass; [i] vinblastine, bleomycin, cisplatin, cyclophosphamide, and dactinomycin; [j] 28% with surgery of residual disease; [k] methotrexate, bleomycin, vincristine, and cisplatin; [l] 24% confirmed by surgery; [m] 16% after resection of residual mass; [n] including 2 patients after surgery of residual mass; [o] only 34 patients considered for response; [p] 11% after surgery

Table 2 Characteristics of studies using high-dose chemotherapy

Author/ year	Type of study/ quality score	N[b] pts/ primary testicular site (%)	Histology % (S vs NS/ mixed)	Second line (%)	≥3rd line (%)	Refractory/ HDCT (%)	Schedule	ORR (%)	Toxic deaths (%)	Median OS (months)	1y OS (%)	2y OS (%)	3y/5y OS (%)
Adra/ 2016	Retrospective	341/87	22 versus 78	83	17	32/0	SDCT x1–2[a] → CBDCA + VP16 x2 + PBSCT → ±VP16 maintenance (37%)	–	26.4	Not reached	80	66	63/60
Agarwala/ 2011	Retrospective	48/–	100 versus 0	50	50	–/0	VIP x1[b] → CBDCA + VP16 x2 + PBSCT	75 (CR)	6.2	Not reached	85	79	79/75
Ayash/ 2001	Phase 1–2	29/100	17 versus 83	10	90	34/0	CBDCA + VP16 + ABMT or PBSCT x1–2	39 ($n = 26$)[c]	10	14	65	40	40/40
Berger/ 2014	Retrospective	95/68	18 versus 74	100	0	–/0	CBDCA + VP16 + PBSCT x3	60	4	73	83	68	55/40
Broun/ 1994	Prospective	23/100	–	100	0	–/0	VIP or PVB x2 → CBDCA + VP16 x1 + ABMT	83 ($n = 18$)	4.3	16	–	–	–/–
Broun/ 1997	Phase 2	25/100	16 versus 84	100	0	12/0	±PVB or PEI or VIP x1–2 → CBDCA + VP16 + ABMT ± PBSCT x2	88[d]	4	19.5	–	–	–/–
De Giorgi/ 2011	Retrospective	100/88	3 versus 96	61	39	19/0	CBDCA + VP16 ± CTX or IFO x1–2 + ABMT or PBSCT	50	12	11	48	39	35/35
Einhorn/ 2007	Retrospective	184/–	19 versus 81	73.4	26.8	21.7/0	±VIP → CBDCA + VP16 x1–2 + PBSCT	–	1.6	Not reached	80	75	72/68
El-Helw/ 2006	Retrospective	33/76	18 versus 79	49	51	30/0	CBDCA + VP16-based x 1–2 + PBSCT	71 ($n = 31$)	6	–	–	60	–/57
Lampe/ 1995	Retrospective	23/95	13 versus 87	43	57	13/0	Platinum-based CT → CBDCA + VP16 x 1–2 + ABMT	63 ($n = 19$)	4.3	–	–	–	–/–
Lorch/ 2010	Retrospective	49/92	10 versus 89	0	100	18/0	Platinum-based CT → CBDCA + VP16-based x1–2 + PBSCT	55	2	–	68	40	33/17
Lyttelton/ 1998	Prospective series	31/–	19 versus 81	0	100	70/0	CBDCA + VP16 + CTX x1 + PBSCT	–	3	12	50	47	41/40
Necchi/ 2016	Retrospective	46/63	100 versus 0	30.4	43.5	21.7/0	CBDCA + VP16-based x1–2 or 3	–	0	Not reached	75	70	70/60
Margolin/ 1996	Prospective	20/50	5 versus 95	40	60	0/0	CBDCA + IFO + VP16 + ABMT or PBSCT x2	–	0	24	65	52	52/52
McNeish/ 2004	Prospective	36/100	27 versus 73	0	100	19/81	PAC + CBDCA + VP16 + CTX x1 + PBSCT	–	16.6	32.2	68	58	50/50
Rick/1998	Retrospective	150/80	8 versus 92	63	28	25/0	CBDCA + VP16 + IFO x1 + ABMT or PBSCT	55[e]	3	–	60	48	44/44
Rosti/ 2002	Retrospective	84/90	3.5 versus 96.5	8	92	–/0	CTX/VIP/PEI → CBDCA + VP16 + ABMT or CBDCA + VP16 + IFO + ABMT CBDCA + VP16 + CTX x1 + PBSCT	45	11.9	15	57	37	32/30
Vaena/ 2003	Retrospective	80/74	5 versus 87	54	46	70/0	CBDCA + VP16 or CBDCA + IFO + VP16 x1–2 + ABMT or PBSCT	45[f] ($n = 63$)	6.2	14.7	58	40	37/35
Nichols/ 1992	Phase 2	40/61	–/–	13	87	50/0	CBDCA + VP16 x1–2 + ABMT	45	13	7.6	35	–	–
Siegert/ 1994	Phase 1/2	74/77	–/–	8	92	32/0	CBDCA + VP16 + IFO x1 + ABMT	63	3	22	56	44	–
Beyer/ 1995	Randomized	47	–/–	–	–	30/0	CBDCA + VP16 + IFO x1 + PBSCT versus ABMT	75	2.2	–	–	–	–

Table 2 continued

Author/year	Type of study/quality score	N[b] pts/primary testicular site (%)	Histology % (S vs NS/mixed)	Second line (%)	≥3rd line (%)	Refractory/HDCT (%)	Schedule	ORR (%)	Toxic deaths (%)	Median OS (months)	1y OS (%)	2y OS (%)	3y/5y OS (%)
Motzer/1996	Phase 2	58/86	7 versus 93	17	83	56.9/0	CBDCA + VP16 + CTX x1–2 + ABMT	100	12	11	42	31	25/25
Motzer/2000	Phase 1/2	37/70	11 versus 89	78	22	0/0	PAC + IFO X 2 → CBDCA + VP16 x3 + PBSCT	62	0	Not reached	65	55	55/–
Rick/2001	Phase 2	80/84	–/–	67	33	13/0	TIP X 3 → CBDCA + VP16 + thiotepa x1 + PBSCT	66	*1.25*	13	57	40	30/–
Pico/2005	Phase 3	263/83.6	9.1 versus 90.9	100	0	0/0	PEI/VeIP X 4 versus PEI/VeIP x3 + CBDCA + VP16 + CTX x1 + PBSCT	75	*7*	40	72	56	52/50
Lotz/2005	Phase 2	45/75.6	11 versus 89	15.5	84.5	15.5/0	EPI + PAC → thiotepa + CTX x1 + CBDCA + VP16 + IFO x2 + PBSCT	37.7	11.1	11.8	43	24	23.5/–
Margolin/2005	Phase 1/2	43/–	11.6 versus 88.4	7	93	–/0	PAC → CBDCA + VP16 x1 or IFO x2 + PBSCT	NR	3.2	15	68	42	42/42
Feldman/2010	Phase 1/2	107/67	12 versus 88	76	24	74/0	PAC + IFO → CBDCA + VP16 x1 + PBSCT	58	1.9	Not reached	66	55	52/52
Lorch/2012	Randomized	211/89.6	19.4 versus 79.6	85.8	14.2	24 versus 19/0	VIP X 1 + CBDCA + VP16 x3 versus VIP X 3 + CBDCA + VP16 + CTX x1 + PBSCT	75.9 versus 62.1	4 versus 16	78 versus 20	80 versus 61	58 versus 50	52 versus 42/49 versus 39
Selle/2014	Phase 2	45/88.6%	35.6 versus 64.4	73.3	22.2	0/0	EPI-PAC → thiotepa-PAC x1 + CBDCA + VP16 + IFO x2 + PBSCT	48.8	4.4	32	70	66	46

PBSCT peripheral blood stem cell transplantation, *VIP* vinblastine + ifosfamide + cisplatin, *CBDCA* carboplatin, *NR* not reached, *PEI* cisplatin + etoposide + ifosfamide, *ABMT* autologous bone marrow transplantation, *CTX* cyclophosphamide, *VP 16* etoposide

[a] Only platinum-sensitive disease; [b] only not refractory or first line; [c] 4 patients after surgery; [d] 8 patients received surgery of residual mass; [e] 24% after further surgery of residual mass; [f] 6% after surgery

Table 3 Clinical outcomes in studies

Outcome	Standard-dose chemotherapy	High-dose chemotherapy	*P* value (Chi-square test)
Pooled ORR (%)	51.6	62.4	0.026
Median OS (months)	14.8	24.09	0.09 (*T* test)
Pooled mean 1-year OS (%)	64.2	63.7	0.9
Pooled mean 2-year OS (%)	63.6	51.2	0.4
Pooled mean 3-year OS (%)	45.1	46.7	0.75
Pooled mean 5-year OS (%)	43	45	0.6

OS overall survival, *ORR* overall response rate

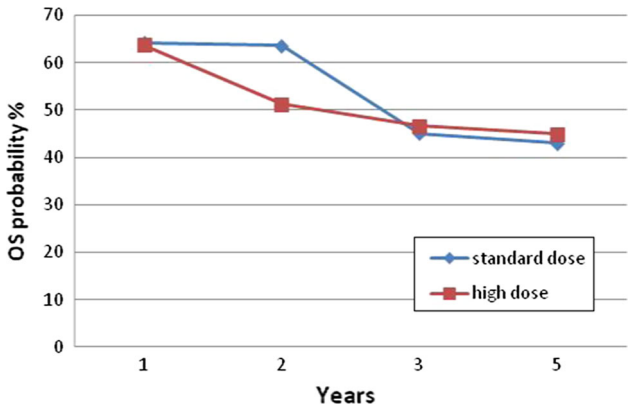

Fig. 2 Survival curves of pooled overall survival in standard-dose and high-dose chemotherapy

Second-line studies only

Among second-line studies with data available, the pooled mean OS was 23.4 versus 39.7 months for standard-dose CT and HDCT (Chi-square, $P = 0.14$). The pooled means for 1-, 2-, and 3-year OS were 70 and 73% ($P = 0.6$), 56.5 and 61% ($P = 0.4$), and 52 and 55% ($P = 0.7$), for standard-dose CT and HDCT, respectively.

Studies with at least two planned HD transplants

Eight studies included two or more transplants among HDCT studies. The pooled median ORR was 68%. Overall, the mean 1-, 2-, and 3-year OS rates were 71, 56.8, and 51.9%.

Discussion

Testicular cancer is highly curable in both early and advanced disease, with cure rates approaching 70–80% even in the metastatic stage. Platinum-/etoposide-based (PEB) CT is the standard first-line therapy for advanced disease. For patients relapsing after upfront therapy or refractory to platinum-based CT, salvage regimens such as VIP, TIP, PEI, or VeIP are the currently available treatments. These chemotherapies were used from 2000s with a 2-year OS rate of near 80% and an ORR of about 80% [3–5]. To our knowledge, our study is the first systematic analysis that compares the standard and HD chemotherapy regimens used for the treatment of relapsed GCTs after first-line therapy. In this large systematic review of relapsed or refractory GCTs, we found that there were no significant differences in efficacy, whether comparing 1-, 2-, 3-, and 5-year OS rates, with a minimal, albeit significant, benefits in ORR for HDCT. Median OS not significantly favored HDCT series by about 10 months, even if HDCT studies included more pretreated patients. It is conceivable that some amount of patients (such those progressing after a conventional second-line CT) could be salvaged with a third-line HD CT program. However, we did find that HDCT use was associated with higher rates of treatment-related mortality compared to standard-dose CT.

Traditionally, clinical trials with novel agents and HDCT with PBSCT have been considered alternative options, in particular for refractory/poor risk patients [54] or for those that relapse after the traditional second-line therapies mentioned above. Disadvantages of HDCT are the lack of available referral centers for the HD management and the higher risk of mortality (1.29% for standard CT vs. 6.46% for HDCT). Unfortunately, there is no definitive reason to prefer standard-dose CT or HDCT in relapsed GCTs, and only one randomized trial exists in the literature comparing standard-dose CT plus or minus consolidation with CBDCA–etoposide-based HDCT. In that trial, Pico et al. [6] showed similar ORR, event-free survival, and 3-year OS between HDCT consolidation and conventional (ifosfamide-based) CT. Even after adjustment for prognostic classification and tumor markers, the results were not different. This study, however, included only patients that responded to induction standard-dose CT and were offered HDCT as consolidation therapy.

In this analysis, even including late salvage regimens used as third-line therapy or beyond, the overall pooled median OS at 2 and 3 years is about 50% for both treatment types, even though the cure rate is still unsatisfactory, with half of the patients dying of the disease. A prognostic model has

been developed from a retrospective database analysis of various European centers [63]. In this database of more than 1500 patients (mainly of non-seminoma histology) treated with standard-dose CT or HDCT, the 3-year OS ranged from 6 to 77% in low- to very high-risk subgroups (median 58%). These figures are nearly identical to our second-line subgroup analysis (pooled 3-year OS of 52–55% for both arms). However, our analysis and the Lorch et al. database [63] did not answer the question of which first and second salvage treatment is the best in relapsed GCT. In the large retrospective analysis performed by Lorch et al. in 2011 [7], HDCT was found to be superior, in particular in intermediate- to high-risk patients (those with unfavorable risk factors such as progression-free interval, site of metastases, extragonadal vs. gonadal primary, levels of tumor markers, response to first-line therapy, and histology).

Our analysis comprised mainly patients with non-seminoma histology and with primary gonadal cancers. Two studies reported outcomes of testicular seminoma, either with standard-dose or with HDCT with a similar outcome (3-year OS, 60%). Refractory patients (those relapsing or progressing during or within 1 month after their initial platinum-based chemotherapy regimen) are also included in the series presented in this review with a wide range of patients enrolled. Three studies in the standard-dose arm and five studies in the HDCT arm included more that 70% refractory patients with similar 3-year OS rates (47 and 57%, respectively). These refractory patients generally have a poor prognosis; however, treatment can still be beneficial in selected cases. In Einhorn's study [27], HDCT in refractory patients rendered 45% of them disease free, compared to 68% of those with platinum-sensitive disease. As for other patients with relapsed or refractory disease, patients with platinum-refractory disease should be referred to a cancer center with expertise in GCTs. Finally, an analysis of third-line or beyond settings for treatment (considering inclusion of at least 70% of patients in this setting as criterion) was performed, with the inclusion of 21 studies with heavily pretreated subjects. In this setting, median and 3-year OS were 12 months and 44% with standard-dose CT and 15 months and 43% in HDCT trials. Conventional drugs used after multiple relapses are gemcitabine, oxaliplatin, and paclitaxel, either as doublet or as triplet regimens. In these subjects, long-term survivors are at risk of late toxicities and death as a result of causes other than GCT, as reported by Lauritsen et al. [64].

The present analysis has some inherent limitations related to our retrospective and indirect comparison. First, our research was not based on individual patient data, but rather on the information available in publications. Additionally, given the retrospective and non-randomized nature of our studies, there is significant heterogeneity between the studies analyzed, and this could have potentially affected the results. We tried to limit the impact of this variation by excluding small studies and studies presented only in abstract form. Also, median OS was not reported in 16 studies due to limited follow-up or a low number of events. Finally, an inherent limitation is that clinical trial patients are typically younger and more fit than in the real-world setting in peripheral centers and this should be taken into account when generalizing the results to the overall patient population encountered in clinical practice. Our study, however, evaluated 4228 patients who had undergone CT with standard or HD regimens for relapsed/refractory GCT, and this is by far the largest analysis to date examining this topic. The topic of second-line therapy in testicular cancer is far from obtaining a definitive answer from the data published so far. An ongoing randomized phase 3 trial (TIGER) will provide an OS comparison between TIP and paclitaxel–ifosfamide followed by three cycles of HD CBDCA–etoposide in progressing/recurrent GCTs.

In conclusion, our systematic review shows that testicular cancers could be successfully treated with both standard-dose CT and HDCT (plus or minus surgery for residual disease) in second-line or further salvage settings. In 59 studies including both second-line therapies or beyond, almost half of patients were still alive at 3 years, with a trend for better median OS in HD studies but similar rates of long-term survivors at 5 years. In patients with refractory disease, the prognosis is still unsatisfactory.

Continuous referral to excellent and specialized centers and participation in clinical trials after a first or second relapse should continue to be a priority, and the need for new agents is urgent.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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