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HSCT FOR SOLID TUMORS

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INTRODUCTION

High-dose chemotherapy (HDCT) with stem-cell support is a procedure that allows the administration of high doses of chemotherapy that would be lethal otherwise. In HDCT, extra-medullary toxicity is the dose-limiting factor. Use of peripheral blood stem cells and improvement in patient management has reduced non-relapse mortality to less than 5%. Over the last decades, knowledge about HDCT in solid tumors has increased, particularly in breast, ovary, lung, and germ cell tumors (GCT)[1–3]. Allogeneic hematopoietic stem-cell transplantation (HSCT) has also been explored, especially in advanced kidney cancer[3].

HIGH-DOSE CHEMOTHERAPY (HDCT) FOR GERM CELL TUMOR (GCT)

Recommendation: HDCT should not be offered for frontline therapy in germ cell tumors (Level of Evidence 1b, Grade of Recommendation A).

Recommendation: HDCT should be offered as second or third-line therapy of germ cell tumor, even in patients with mediastinal, platinum-refractory, or non-seminomatous GCT (Level of Evidence 2b, Grade of Recommendation B).

Recommendation: Conditioning regimen should be carboplatin and etoposide (Level of Evidence 1b, Grade of Recommendation A).

Recommendation: Two or three cycles of HDCT should be offered instead of one (Level of Evidence 1b, Grade of Recommendation B).

Recommendation: For patients with residual disease following HDCT, surgical resection should be performed (Level of Evidence 4, Grade of Recommendation C).

Testicular malignant tumors are the most frequent solid tumor of the young male, and 95% of these are germ cell tumors (GCT)[4]. They are unique tumors in which they represent a malignant transformation of a totipotent germ cell. They are divided, histologically, in seminoma and nonseminoma. Both secrete beta-human chorionic gonadotropin (beta-HCG), while only the latter produces alpha-fetoprotein (AFP). Approximately 75% of the patients are cured with conventional5. Follow-up includes serial image exams and of the serum markers HCG e AFP.

FRONTLINE HIGH-DOSE CHEMOTHERAPY

Frontline HDCT is not recommended. There are four randomized trials (an Italian[6], a French[7], an American phase III[8], and a European phase III[9]) that have not shown a benefit of HDCT in high-risk patients. In the American trial, however, there was a trend towards better response in patients with unsatisfactory tumor marker response (61% CR with 1-y duration, against 34%, p=0.03). A systematic review that included phase III and phase II trials showed no overall survival benefit in patients with unsatisfactory serum marker response[10].

RELAPSE AND REFRACTORY DISEASE

A unique characteristic of germ cell tumor management is that conventional chemotherapy can cure relapsed patients. A large series is frequently cited for comparison[11]. In this series, relapsed and refractory patients were treated with vinblastine, ifosfamide, and cisplatin (VeIP). Fifty percent reached a complete response, and 24% were long-term disease-free.

Diagnosis of relapsed/refractory disease is not always straightforward. Patients with residual disease and persistently high AFP or HCG markers frequently have irresectable viable cancer and should undergo chemotherapy instead of surgery. On the other hand, radiologic progression paradoxically associated with adequate decline of serum markers can occur with teratoma growth syndrome, which should not be interpreted as progression[12]. Teratoma is insensitive to chemotherapy, and residual lesions should be resected. Likewise, lung nodular lesions, especially subpleural, can be induced by bleomycin. Moreover,

marijuana can lead to a rise in HCG, and a rise in luteinizing hormone secondary to hypogonadal status may interfere with the HCG test.

Patients whose diseases progress during frontline therapy or within 4 weeks of the last dose of chemotherapy (platinum-refractory) are a poor-prognosis group of patients. Patients with seminoma have a better prognosis, as well as those with testicular or retroperitoneum relapse. Patients with mediastinal disease are another group of poor prognosis. Patients with an incomplete response, who are platinum-refractory, or primary mediastinal site have less than 10% overall survival in 10 years[13,14].

HIGH-DOSE CHEMOTHERAPY IN RELAPSED/ REFRACTORY PATIENTS

High-dose chemotherapy is the second-line treatment of choice in many institutions, despite the lack of positive randomized trials. The chemosensitivity of GCT, the marked dose-response effect, the extremally low incidence of bone marrow metastasis, and the young age of these patients make HCT very attractive.

First phase I and II studies, from Indiana University[15] and the Eastern Cooperative Oncology Group[16], have shown that 15-20% of patients with multiple relapses can be cured. In the Indiana series, all long-term surviving patients received two cycles of HDCT, and 75% of the patients with partial remission achieved complete remission after the second cycle. These studies underline the importance of surgery in patients with residual disease following HDCT.

Subsequent studies focused on drug-dose escalation[17], establishing the maximal tolerated dose Carboplatin 2,100 mg/m2 and Etoposide 2,250 mg/m2. Marked reduction of non-relapse mortality was achieved with peripheral blood stem-cells.

There is only one phase III trial of HDCT in relapsed GCT[18]. In this study, 280 patients were randomized to receive 4 cycles of conventional chemotherapy or 3 cycles followed by HDCT. There was no difference in disease-free or overall survival. This study has been criticized by the low power, the toxic conditioning regimen, and the one-HDCT cycle. A systematic review supports the need for at least 2 cycles of HDCT10.

The greatest evidence of benefit of HDCT comes from a registry study[19], which included more than 1,500 patients and showed a lower risk of death in first-relapse patients who received HDCT (HR=0.65, 95%CI 0.56-0.75). In subgroup analyses, nonseminoma and low-risk patients seemed to not benefit. These results were confirmed in a retrospective analysis of the German Testicular Cancer Study Group[20]. Moreover, this study shows that more than 70% of relapsed patients undergo HDCT in second-line therapy, making comparisons more difficult.

Currently, the best reported results are from the Indiana University[21] and the Sloan-Kettering Cancer Center[14].

The Indiana University [21,22] performs two HDCT cycles with Carboplatin 2,100 mg/m2 and Etoposide 2,250 mg/m2 followed by oral etoposide maintenance. With a median follow-up of 40 months, progression-free survival was 40%. Interestingly, half of the patients with platinum-refractory or third-line patients had an excellent response.

The Memorial Sloan-Kettering Cancer Center[14] performs three cycles of HDCT with Carboplatin and Etoposide. 5-y overall survival was 52%. Most patients were platinum-refractory. Long-term overall survival for patients with mediastinal disease was 24%.

CONDITIONING REGIMEN AND SEQUENTIAL THERAPY

The role of sequential HDCT and the addition of a third drug have been studied.

The German Testicular Study Group[17,23] compared one cycle of HDCT with three cycles. A third drug was added to the group that received one cycle, but the mortality was significantly higher (16 versus 4%), and the study was halted.

Grossi et al[24], in a prospective study that included all patients treated in Switzerland, have not found differences in outcomes between 2 or 3 cycles of HDCT, while 1 cycle seemed to yield inferior results. In subgroup analysis, the third cycle of HDCT seemed to benefit patients who achieved a complete response after the first cycle. DeFilipp[25] also found no difference between 2 or 3 cycles of HDCT.

In a large registry study[19], 5-y overall survival was significantly higher in patients who received sequential HDCT (61% versus 46%, p<0.001) and in those who received Carboplatin and Etoposide conditioning (62%, against 35% with +Ifosfamide, 44% +Thiothepa, 56% +Cyclophosphamide, p<0.001).

An EBMT registry study[26] suggested that non-relapse mortality is lower with Carboplatin and

Etoposide conditioning regimen for patients older than 40 years.

A systematic review[10] suggests that at least two cycles of HDCT should be offered, and a single cycle should not be used.

An EBMT study[27] showed that the rates of secondary malignancies are 4.2% (solid tumor) and 1.4% (hematologic malignancy).

POST-HDCT RESIDUAL MASS

Surgical resection of residual masses plays an important role, contributing to the cure. In a German retrospective analysis[28], viable tumor cells were found in 46% of the patients, and event-free survival in 5 years was 38%. In patients with viable cancer, there is no benefit in chemotherapy. Progression and relapse following HDCT have a dismal prognosis, and in the Indiana series[29] only patients who received surgical treatment were alive.

Graft product contamination

Tumor cells can be identified in up to half of the apheresis-collected grafts, but its importance is unknown. Results are contradictory. In one of them, there was no difference between the groups[30], in another all patients with detectable tumor cell relapsed[31], and in the third no patients with undetectable tumor relapsed[32].

HIGH-DOSE CHEMOTHERAPY FOR OTHER SOLID TUMORS

Recommendation: HDCT should be offered for ovarian germ tumor or gestational trophoblastic tumor, chemorefractory (Level of Evidence 4, Grade of Recommendation C).

Recommendation: HDCT should not be offered to any kind of breast cancer (Level of Evidence 1a, Grade of Recommendation A).

Recommendation: HDCT should not be offered for ovary or lung cancer (Level of Evidence 2b, Grade of Recommendation B).

Recommendation: HDCT should be offered to patients with high-risk localized Ewing sarcoma (Level of Evidence 1b, Grade of Recommendation A). HDCT can be offered for relapsed Ewing sarcoma (Level of Evidence 2a, Grade of Recommendation B)

High-dose chemotherapy in ovarian cancer

HDCT was tested in refractory and chemosensitive ovarian cancer[33–38]. Despite initial response, short remission was documented, and no benefit was observed[36–39]. For patients with relapsed ovarian germ cell tumors, HDCT can be curative [40,41].

High-dose chemotherapy in lung cancer

Small cell lung cancer is an extremally chemo- and radio-sensitive disease, with response rates of 80%. Few patients are cured however2. Results with HDCT were disappointing, and the procedure was abandoned[42,43].

High-dose chemotherapy in breast cancer

The role of HDCT in breast cancer remains controversial despite more than 20 years of experience. Two meta-analyses of randomized trials[44,45] have not found survival benefit in HDCT. Recently, in a subgroup analysis, Steenbruggen et al[46] suggest there might be a benefit for patients with 10+ positive lymph nodes or with triple-negative breast cancer. These results, however, must be confirmed in appropriately designed clinical trials.

High-dose chemotherapy for gestational trophoblastic neoplasia

Gestational trophoblastic disease is a heterogeneous group of diseases that arise from the abnormal proliferation of the placental trophoblast, i.e., of the fetal tissue. It includes, among others, choriocarcinoma, trophoblastic tumor, and invasive mole. Beta-HCG may be high. Case reports and case series reported cure with HDCT[47–50].

High-dose chemotherapy for Ewing sarcoma

Overall survival of Ewing sarcoma patients with conventional therapy ranges between 9 and 41%. Patients with high-risk localized disease benefited from frontline HDCT[51]. High-risk disease was defined as poor histologic response (≥10% viable cells), large tumor volume at diagnosis (≥200 mL), or small tumors with poor radiologic response (<50% reduction). In patients with pulmonary metastases, no benefit was seen[52]. A systematic review of observational studies suggests that relapsed patients might benefit from HDCT[53].

Allogeneic stem cell transplantation in solid tumors

Recommendation: There is no data to recommend allogeneic stem-cell transplantation in solid tumors in any setting.

TABLE 1 - Selected conditioning regimens

Institution	Carboplatin	Etoposide	Cyclophosphamide	# Transplants
MSKCC14,54dose-intense chemotherapy with paclitaxel and ifosfamide followed by carboplatin and etoposide (TICE	AUC=24	1,200mg/m2	x	3
Indiana16 *	2,100mg/m2	2,250mg/m2	x	2
MSKCC55	1,500mg/m2	1,200mg/m2	150mg/kg	2
Germany56	1,500mg/m2	1,500mg/m2	x	3
	Cisplatin	Etoposide	Ifosfamide	# Transplants
EORTC9etoposide, and ifosfamide (VIP	100mg/m2	1,500mg/m2	12,000mg/m2	3

*etoposide oral maintenance 50mg/day x 21 days every 4 weeks for 3 cycles

TABLE 2 - High-dose chemotherapy in relapsed/refractory GCT patients

Institution	#Patients	%CR	%Alive and disease-free	Follow-up	TRM
MSKCC55	58	40	21	28 months	12%
Indiana15	40	30	15	> 24 months	18%
Germany57230 patients were planned to be recruited in a prospective, randomized, multicenter trial comparing one cycle of cisplatin 100 mg/m2, etoposide 375 mg/m2, and ifosfamide 6 g/m2 (VIP	74	50	38	48 months	3%
MSKCC58which had been identified previously as favorable prognostic factors to conventional-dose salvage chemotherapy.\nRESULTS: Thirty-two (70%	84	56	50	58 months	NA
Indiana21	184	NA	63	48 months	3%
ECOG16	38	24	13	> 18 months	13%
Europe18	109	26	31	45 months	7%
Germany59	176	15*	34	> 60 months	NA
Germany28postchemotherapy resections of residual tumors were performed in 57 patients who had been treated with HDCT for relapsed or refractory GCT and who had achieved a partial remission to this treatment.\nRESULTS: Complete resections of residual masses were achieved in 52 (91%	211	22**	43	36 months	9%
MSKCC14	107	42***	53	> 60 months	2%

CR: complete remission; TRM: Transplant-related mortality. NA: Not available
* 38% in total, when included patients who underwent posttransplant surgical resection
** 37% in total, when included patients who underwent posttransplant surgical resection
*** 50% in total, when included patients who underwent posttransplant surgical resection

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