Role of conventional salvage multiple-drug chemotherapy in relapsed and refractory aggressive non-Hodgkin lymphomas

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Abstract. Autologous stem cell transplantation is the standard care for patients with relapsed or refractory aggressive non-Hodgkin lymphomas. Of the patients who are sensitive to second-line chemotherapy, approximately 40-50% are likely to be cured using this approach. The optimal salvage regimen for pre-transplant debulking is controversial and these second-line chemotherapies are particularly important for patients who cannot undergo transplantation for various reasons including age, comorbidity and insufficient stem cell collection. Numerous reports regarding this topic are available. This study evaluated reports published in the last 5 years, focusing on conventional multiple-drug second-line chemotherapies (with or without rituximab), and disregarding single-agent investigational phase-II trials. Results are encouraging, particularly when considering that the more recent and less toxic combinations appear to be equivalent to or even more favourable than previous, more aggressive approaches. Previous results obtained using a combination of mitoxantrone, carboplatin, cytarabine and methylprednisolone, are further updated and included in this study. In conclusion, the most effective conventional chemotherapy currently available for patients with relapsed or refractory non-Hodgkin lymphomas obtains complete remission rates of up to 50-70%; the achievement of a complete remission is the most important factor associated with a better outcome. Although the addition of rituximab is beneficial and safe, it is more effective in patients who have previously not been exposed to this monoclonal antibody. The addition of cycles of salvage chemotherapy to those strictly required for mobilization of peripheral blood stem cells ultimately improves the response rate.

Introduction

Histologically aggressive types of non-Hodgkin lymphomas are considered to be among the disorders most sensitive to chemo-therapy and radiotherapy. However, a substantial fraction of patients (40-50%) with such disorders fail to achieve complete remission on first-line treatment (1,2). Approximately 10% of the subjects develop progressive disease during their initial therapy, and must be considered as truly refractory patients. Moreover, approximately 50% of complete responders eventually relapse. The prognosis of these patients is generally poor. The improvement of transplantation techniques has enhanced the outlook for nearly 50% of refractory or relapsed patients using high-dose chemotherapy (HDC), followed by autologous (ASCT) or allogeneic (Allo-SCT) stem-cell transplantation (3). Nevertheless, the response to transplantation procedures depends on a number of factors such as presentation of the disease, type and number of previous therapies, prognostic factors, response to debulking chemotherapy regimens administered before HDC and the type of pre-transplant conditioning regimen used. Chemosensitivity to the disease prior to bone marrow transplantation has been shown, in particular, to be a significant discriminator of the final outcome, with complete disappearance of symptoms. According to certain authors (4), patients who do not respond to second-line (salvage) chemotherapy should not be offered ASCT, but should be candidates for alternative or experimental therapies. However, if their response to salvage therapy is excluded, HDC is not a viable treatment option for all refractory or relapsed patients. There are various reasons for this, including comorbidity, frailty, advanced age and risk of complications. Therefore, these patients must be maintained in an acceptable clinical condition and their life prolonged with conventional chemotherapy. Chemotherapy protocols have been designed for pre-transplant cytoreduction and complete remissions have been achieved in a significant number of cases.

This study provides a brief overview of the conventional multiple-drug regimens that have recently been designed and tested to improve the outlook of patients with relapsed or refractory aggressive non-Hodgkin lymphoma.

Materials and methods

Numerous studies, as well as bibliographic references, have reported on the treatment of relapsed or refractory aggressive non-Hodgkin lymphomas. In this study, the field of interest was restricted to clinical studies published in the last 5 years. These studies included at least 10 patients who either had histologically aggressive types of non-Hodgkin lymphomas or

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findings regarding those patients with aggressive lymphomas were able to be extrapolated. Phase II studies with single-drug therapy (with cytostatic or biological agents) were excluded, even in the case of promising results, since results from any comparison and possible implementation with conventional drugs were inconclusive. Studies employing radio-immuno-conjugates were also excluded since these drugs are limited to the investigational setting, show marked myeloablative effects, and their administration remains confined to selected, well-experienced centers.

The parameters selected to evaluate and compare the effectiveness of the salvage regimens and the value of the reports were: number of patients evaluated, median or range (or both) of the number of chemotherapy lines previously administered, overall response rate (ORR, i.e., the cumulative percentage of partial and complete remissions), complete remission rate [CRR, which is the best prognostic discriminant, particularly in relapsed or refractory patients (5)], number of cycles administered and power of peripheral blood stem cell (PBSC) mobilization (+, sufficient for an autologous stem cell transplant but <6x10^6/kg CD34$^+$ cells, and ++, >6x10^6/kg CD34$^+$ cells).

A previous study reported on a favourable response rate to an outpatient regimen, i.e., the MJMA schedule using the combination of mitoxantrone, carboplatin, cytarabine and methylprednisolone (6). In this study, the results of the previous series of patients are updated. Subsequently, 4 cases with Hodgkin lymphoma were excluded and 3 further patients with diffuse large B-cell lymphoma were included. Two of the latter patients had relapsed following R-CHOP and 1 was refractory to R-CHOP. The number of patients with aggressive non-Hodgkin lymphomas treated with the salvage MJMA regimen was 27. The outcome of the 27 patients is included.

The MJMA chemotherapy was a 3-day, shortened and intensified variant, with a 3-week interval of the known 5-day MiCMA regimen that is delivered at 4-week intervals (7,8). The modifications were made to increase the dose size of carboplatin and the dose intensity of all the drugs, while maintaining the feasibility of the treatment in an outpatient setting and without modifying the cumulative doses administered. The schedule revised in this way consisted of mitoxantrone 10 mg/m^2 intravenously (i.v.) on Day 1, carboplatin 200 mg/m^2 daily i.v. on Days 1 and 2, cytarabine 2000 mg/m^2 i.v. on Day 3 and methylprednisolone 500 mg/m^2 daily i.v. on Days 1-3. Treatment was repeated at 21-day intervals for a total of 4-6 cycles. The theoretical mean dose intensity of all the drugs was increased by 25% and the dose size of carboplatin was doubled.

Results

Table I shows the data relating to 35 distinct studies and 1,558 patients. CRR, one of the most reliable indicators of effectiveness, ranges from 14 to 79%, while ORR varies from 28 to 94%.

In our updated series of 27 non-Hodgkin patients included in Table I (17 with relapsed disease and 10 refractory prior to treatment), 18 (64%) achieved complete remission (12 relapsed, 6 refractory) and 8 (30%) obtained only a partial remission (4 relapsed, 4 refractory). ORR was 94% with only 1 patient, who had been refractory to four previous chemotherapy regimens, not responding to MJMA.

The 27 patients experienced severe hematological toxicity (grades 3 and 4 of the WHO scale). Severe neutropenia was observed in all 22 patients and severe thrombocytopenia in 19 of 27 patients. Anemia, with a hemoglobin concentration <8 g/ dl (WHO grade 2) was noted in 6 patients. Of the 27 patients, 18 (aged 27-64) for whom consolidation therapy with HDC and subsequent peripheral blood stem cell (PBSC) rescue was judged appropriate and feasible, underwent marrow stimulation with granulocyte colony-stimulating factor after one of the first three cycles (300 μg every 12 h from Day 5 until completion of the leukapheresis procedures). Mobilization of PBSC was successful in these patients, with a mean yield of CD34$^+$ cells of 10.45x10^6/kg per patient (range 3.70-24.88). A single leukapheresis was sufficient in 15 of 18 patients, while two leukaphereses were necessary in the remaining 3.

Discussion

An effective salvage therapy for non-Hodgkin lymphoma should have low hematological and non-hematological toxicity and good power to mobilize PBSC. Additionally, and most importantly, this therapy should exhibit sufficiently strong cytoreductive activity in order for an adequate number of cycles to be administered, with favourable results, in patients who cannot undergo ASCT.

As noted in Table I, none of the presently available regimens fulfills these prerequisites. Chemoresistance poses the main difficulty, as demonstrated by patients whose disease progressed during or soon after front-line therapies and by patients who relapsed early following such therapies. Findings regarding salvage therapy should refer not only to the number of refractory cases presented, but should also list outcomes separately for refractory and relapsed patients. However, studies rarely report on such outcomes.

It must also be considered that patients with refractory or relapsed lymphomas normally show a reduction in tolerance of salvage chemotherapies compared to front-line regimens due to iatrogenic myelosuppression, variable degrees of marrow infiltration by lymphoma, the onset of newly acquired metabolic abnormalities or worsening of those underlying the lymphoma and a number of possible clinical complications. Consequently, drug doses often have to be reduced. Nevertheless, administration of maximum tolerated doses is necessary in order to achieve the maximum response. Finally, randomized trials are difficult to organize in this setting of patients because of the number of clinical variables that play important clinical roles and, theoretically, require many stratifications, such as histology, tumor bulk, response to and number of previous treatments, symptoms and presence of prognostic factors prior to salvage therapy.

The majority of studies noted that a number of the treated patients received HDC, followed by ASCT or Allo-SCT, making it difficult to compare the intrinsic long-term efficacy of the conventional salvage chemotherapy. For this reason, final response was considered, but not survival parameters. However, since HDC is not a viable treatment option for all refractory or relapsed patients due to factors, including comorbidity, frailty, advanced age and risk of infections, these patients must be maintained in an acceptable clinical condition and their life should be prolonged with conventional chemotherapy.

Table I. Overall response and complete remission rate obtained by the salvage regimens tested in recent years.[b]

Regimen (reference)	No. of patients	No. of previous regimens	ORR (%)	CRR (%)	No. of cycles	Mobilization ability
IIVP (IFO, IDA, VP) (9)	49	1-2	76	33	3	n.g.
DICE (Dexa, IFO, CDDP, VP) (10)	35	1	74	31	4	n.g.
IEV (IFO, EPI, VP) (11)	34	1-2	77	64	3	++
IEV-R (IFO, EPI, VP, Rit) (12)	16	1.5 (1-3)	69	38	2	++
IEV (IFO, EPI, VP) (12)	59	1.5 (1-3)	41	19	2	++
IEV (IFO, EPI, VP) (13)	41	1-4	66	27	2	++
ICE (IFO, CBDCA, VP) (14)	75	1.5 (1-4)	89	29	2.8	++
ICE (IFO, CBDCA, VP) (15)	45	2 (1-5)	45	17	3	++
R-ICE (Rit, IFO, CBDCA, VP) (16)	21	≥2 (DHAP)	52	14	3	n.g.
R-ICE (Rit, IFO, CBDCA, VP) (17)	36	1	78	53	3	++
IVAD (IFO, VP, ARA-C, Dexa) (18)	59	1	67	19	2-3	++
GVP (GEM, VRL, Pred) (19)	15	3	53	33	3.2	n.g.
GV (GEM, VRL) (20)	22	1	50	14	3-6	n.g.
GP (GEM, CDDP) (21)	30	1	53	53	3	n.g.
GDP (GEM, Dexa, CDDP) (22)	51	1	49	16	2	++
GDP (GEM, Dexa, CDDP) (23)	24	1	58	21	3	+
ViGePP (VRL, GEM, PCZ, Pred) (24)	66	1-3	46	23	5	n.g.
R-GIFOX (Rit, GEM, IFO, OX) (25)	13	2 (1-4)	77	50	3	+
GEMOX-R (Rit, GEM, OX) (26)	32	1.7	43	34	4	n.g.
GEM-P (GEM, CDDP, m-Pred) (27)	39	2 (1-5)	39	79	21	++
GEM-P (GEM, CDDP, m-Pred, ± Rit) (28)	39	1-3	59	28	2	n.g.
R-GEM (Rit, GEM) (29)	33	≥2	48	24	2	n.g.
DHAP (Dexa, ARA-C, CDDP) (30)	28	1	68	28	2	++
DHAP (Dexa, ARA-C, CDDP) (31)	53	1-3	62	37	3-4	n.g.
DHAP (Dexa, ARA-C, CDDP) (32)	57	1	72	9	2	[a]
DHAP-VIM-DHAP (Dexa, ARA-C, CDDP, VP, IFO, MTX) (33)	101	1	54	n.g.	3	n.g.
R-DHAP-VIM-DHAP (Rit, Dexa, ARA-C, CDDP, VP, IFO, MTX) (33)	101	1	77	n.g.	3	n.g.
ESHAP (VP, m-Pred, ARA-C, CDDP) (34)	22	1-3	63	27	2-4	++
R-ESHA (Rit, VP, m-Pred, ARA-C, CDDP) (35)	94	1 (Rit+)	67	37	3	
R-ESHAP (Rit, VP, m-Pred, ARA-C, CDDP) (35)	69	1 (Rit-)	81	56	3	++
MiCMA (Mito, CBDCA, ARA-C, m-Pred) (36)	85	1-4	70	26	2-3	++
MJMA (Mito, CBDCA, ARA-C, m-Pred) (37)	31	1-3	72	45	5	n.g.
MJMA[a] (Mito, CBDCA, ARA-C, m-Pred) (6)	27	1.5	94	64	5	++
Dexa-BEAM (Dexa, BCNU, VP, ARA-C, MPH) (38)	29	1	28	3	1-2	+
R-EPOCH (Rit, DOX, VP, VCR, CTX, Pred) (39)	50	1.7	68	28	4	n.g.
R-H-CVAD/ R-AM (Rit, CTX, DOX, VCR, Dexa/ARA-c, MTX) (40)	29	1 (1-5)	93	45	5	n.g.
CMC (2-CdA, Mito, CTX) (41)	33	1-2	58	21	4	n.g.
CEMP (CDDP, VP, Mito, Pred) (42)	47	1	34	23	5	n.g.

ORR, overall response rate; CRR, complete remission rate; ARA-C, cytarabine; BCNU, carmustine; CBDCA, carboplatin; 2-CdA, cladribine; CCNU, lomustine; CDDP, cisplatin; CTX, cyclophosphamide; Dexa, dexamethasone; DOX, doxorubicin; EPI, epidoxorubicin; IFO; ifosfamide; MPH, melphalan; m-Pred, methylprednisolone; Mito, mitoxantrone; MTX, methotrexate; PCZ, procarbazine; Pred, prednisone; Rit, rituximab; VCR, vincristine; VP, etoposide; VRL, vinorelbine; n.g., not given; +, ≤6x10^{10}/kg CD34+; ++, >6x10^{10}/kg CD34+. [a]Data of ref. 6 are updated in this review. [b]The number of patients treated, previous regimens administered, cycles given, together with the mobilization ability of PBSC, are also reported.

Three main groups of regimens are identified according to their pivotal drugs or combination of drugs. The first group comprises ifosfamide-based regimens (9-18) that produce complete remission rates ranging from 14 to 64%. The toxicity of these regimes is mainly hematological and they generally allow for the adequate collection of PBSC in the majority of patients. The second group is formed by the gemcitabine-containing regimens, frequently associated with vinorelbine and/or platinum compounds (19-29). These regimens produce complete remission rates ranging from 21 to 43%, and are generally less toxic to bone marrow. Largely due to their lower toxicity, regimes of the second group are often employed in frail cases. Thus, their ability to mobilize PBSC has been tested in fewer studies. However, in those series in which this aspect was explored, the regimens showed favourable mobilization power. The third group comprises regimens containing cytarabine and platinum compounds (6,30-36, La Sala A, *et al*, Riassunti del 35° Congr. SIE, Edimes, Pavia, abs. 297, 1995). The regimes produce complete remission rates ranging from 3 to 64%, have marked hematological toxicity and considerable non-hematological toxicity, but are able to mobilize PBSC.

An additional issue is the role of rituximab in combination with conventional chemotherapy in the salvage setting. As shown by the studies reported in Table I (12,16,17,25,26, 28,29,33,35,37-39), the addition of rituximab to salvage chemotherapy improves the response rate, without decreasing the mobilization and collection of PBSC. Moreover, the original reports provide evidence of the lack of significant toxicity due to the addition of rituximab to salvage chemotherapy. However, in a number of investigations the majority of patients did not previously receive treatment with rituximab. Thus, the conclusions drawn by Martin *et al* (35), appear to suggest that the impact of rituximab in the salvage setting is limited. The authors concluded that prior exposure to rituximab is an adverse prognostic determinant for the efficacy of the same monoclonal antibody on overall and progression-free survival of relapsed or refractory patients. Martin *et al* hypothesized that the refractoriness of the disease observed in patients who receive rituximab during induction therapy questions the role of HDC and ASCT in this particular setting. Subsequently, the issue regarding resistance to rituximab in CD20+ non-Hodgkin lymphomas, remains to be elucidated (42). The serum concentration of the monoclonal antibody, its catabolic rate, surface expression of CD20 receptors, altered intracellular signaling, altered complement functions and defective cell-mediated immunity are potential factors involved in the resistance to rituximab.

Notably, in a limited series of patients refractory to DHAP, which can be considered a strong second-line chemotherapy, the ORR to R-ICE (16) was 52%, with 14% of the patients achieving a complete response. The results of third-line conventional chemotherapy are usually poor. Consequently, patients with an inadequate response to second-line chemotherapy are considered to have a poor recovery rate with subsequent salvage regimens. The novel use of rituximab in the patients treated by Simpson *et al* (16) explains the promising results obtained with R-ICE.

A further, minor bias affecting the comparability of treatments in the series of relapsed/refractory non-Hodgkin lymphomas is the different number of cycles actually administered. Centers strongly oriented towards ASCT often administer only 2 or 3 cycles in order to allow for the optimal collection of PBSC and early performance of the transplant. In these cases, the clinical response to conventional cyto-reductive therapy is evaluated after only 2 to 3 cycles of chemotherapy. In studies that include larger numbers of elderly or otherwise frail patients, who are not eligible candidates for ASCT, more cycles are administered, which may enable better exploitation of the intrinsic anti-lymphoma effectiveness of the salvage regimens. This discrepancy may explain the different results obtained with the same mitoxantrone-carboplatin-cytarabine-methylprednisolone combination of drugs (MJMA and MiCMA stand for the same drugs, since 'J' in MJMA refers to one of the first abbreviations of carboplatin, JM-8, represented by the 'C' in MiCMA). Sica *et al* (7), La Barbera *et al* (8) and Sorà *et al* (36) administered only 2 or 3 cycles of the MJMA regimen and patients received HDC and ASCT soon after harvesting PBSC. Similar to our study, La Sala *et al* (Riassunti del 35° Congr. SIE, Edimes, Pavia, abs. 297, 1995) administered 5 or 6 cycles, followed by 2-4 cycles which were then used for PBSC mobilization and harvesting. In addition, the doubled dose size of carboplatin and the dose intensification of all the drugs administered to our patients may explain the higher response rate of our series compared to that of La Sala *et al*, the number of cycles administered being equal.

In conclusion, with the most effective conventional chemotherapy currently available for relapsed or refractory non-Hodgkin lymphoma, up to 50-70% of patients obtain complete remission. This is of considerable relevance, given that the achievement of complete remission is the most important factor associated with better survival. The addition of rituximab is useful and safe, although likely more effective in patients not previously exposed to the drug. The addition of more cycles of salvage chemotherapy to those strictly required for the mobilization of PBSC improves the response rate.

Acknowledgements

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