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CHEMOTHERAPY OF NON-HODGKIN LYMPHOMA: THE DIFFUSE TYPES

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Abstract: The application of the Rappaport classification for non-Hodgkin lymphoma has allowed for the stratification of histologic subtypes with consistent clinical correlations. Nodularity imparts a favorable prognosis and response to chemotherapy; diffuse patterns are unfavorable. Fifty percent survivals of 5 to 9 years and 1 to 2 years are observed for nodular and diffuse types, respectively. Single agent chemotherapy is ineffective for the diffuse histologies. Combination chemotherapy results in 20 to 80 percent complete remission rates in patients with mixed cell and poorly differentiated diffuse types; median survivals of 1 to 2 years are achieved. The outlook for diffuse histiocytic lymphoma is optimistic: complete remission rates of 50 to 68 percent are achieved. Flattening of the remission duration curve suggests a significant number of these patients are cured of their disease.

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Before 1966, when RAPPAPORT [23] developed a classification for the non-Hodgkin lymphomas (NHL), the histologic features of such tumors were usually divided into three main cytologic groups: lymphosarcoma, reticulum cell sarcoma, and follicular lymphoma. Such terms were not specific for a single disease entity and did not allow for detailed prospective clinicopathologic correlations. The Rappaport classification has made such correlations possible and has provided a common language to clinicians and hematopathologists. The Rappaport classification is based on cellular composition: those with nodular or follicular patterns are so designated by the addition of the term nodular to the cytologic pattern; those tumors without a nodular pattern are designated as diffuse. The application of the histopathological classification of Rappaport and analysis of a large group of previously untreated patients provides significant differences between the histologic subtypes and survival. Of greater significance, however, is the pattern: nodularity implies a favorable prognosis, diffuse pattern an unfavorable prognosis. In a clinicopathologic correlation in 405 cases of NHL, JONES et al. [14] found an actuarial 50 percent survival of 8 to 9 years for patients with mixed cell nodular (MC-N) and poorly differentiated lymphocytic nodular (PDL-N), and a four year 50 percent survival for patients with histiocytic lymphoma nodular (HL-N). In contrast, the corresponding survival for patients with mixed cell diffuse (MC-D) and poorly differentiated lymphocytic diffuse (PDL-D) was less than 2 years; for histiocytic diffuse (HL-D) it was about one year. DUMONT et al. [10], summarizing the experience of 244 patients followed at the Saint-Louis Hospital, reported a 50 percent survival of more than five years for MC-N or PDL-N, but only one year survival for patients with MC-D, PDL-D, or HL-D. BROWN et al. [5], in a retrospective analysis of 460 previously untreated

patients followed at the Princess Margaret Hospital, found a 50-percent survival rate greater than 5 years for MC-N or PDL-N; 4 years for HL-N; 1.5 to 2.5 years for MC-D or PDL-D and 1 year for HL-D. These series, which total 1,109 patients, are summarized in Table I.

The rational management of NHL began in the early 1960's when SKIPPER, SCHABEL and WILCOX [28] demonstrated the quantitative relationship between tumor cell kinetics and chemotherapy in the L1210 mouse leukemia system. Two principles evolved from these studies: the reduction in the log number of total body tumor cells is directly proportional to the amount of drug administered; and a particular drug dose will kill a constant fraction of malignant cells which is independent of the log number of cells present. It was also demonstrated that a single tumor cell would, through numerous doublings, eventually overwhelm the host. Often, clinical evidence of disease was not apparent until 10^9 or 10^{10} cells were present (about 1 gram of tumor). It is evident that the cure of NHL will be achieved more easily if a low tumor burden is present. Furthermore, the treatment must (theoretically, at least) reduce the tumor mass to less than one cell. However, the agents in the chemotherapeutic armamentarium possess low log kill capability. The futility of single agent therapy, as a modality for cure, is at once recognized and the need for combination chemotherapy appreciated. The chemotherapy studies of the last 10 to 15 years support these statements.

In a review of the Stanford University experience with advanced NHL, JONES et al. [15] reported on the results of disease treated with single alkylating agents, or an alkylating agent plus vincristine or prednisone. The complete remission (CR) rate for all patients with nodular disease was less than 40 percent, that for diffuse disease less than 25 percent. Patients with PDL-N achieved a 48 percent complete remission rate, while patients with HL-D achieved

infrequent complete remissions (5 percent). By 1970, it was apparent that patients with advanced NHL with a diffuse pattern had a very unfavorable prognosis which was not greatly altered by single agent therapy. Patients with nodular disease, with a more sedentary natural history, were more likely to respond to single agent therapy.

Combination chemotherapy for advanced NHL, especially diffuse types, was a logical outgrowth of the chemotherapy kinetic studies of SKIPPER et al. [28] and the institution of MOPP (Mustargen hydrochloride®; Oncovin®, procarbazine, prednisone) combination chemotherapy for advanced Hodgkin disease [9]. In view of the encouraging results achieved with combination therapy in patients with Hodgkin disease (70 to 80 percent CR rates), numerous studies with combination chemotherapy for management of NHL were undertaken. Comparison of the early combination therapy trials and even more recent reports is difficult because the Rappaport classification was not applied uniformly. However, CR rates increased from 5 percent to 20 to 80 percent. In most of these programs CVP (cyclophosphamide, vincristine, prednisone) was used with a variety of dose and time schedules. Unfortunately, few of these studies separated the nodular and diffuse patterns for individual assessment of remission rates. Thus, many of the studies summarized in Table II include patients with nodular patterns, and the complete remission rate is actually higher than if only diffuse patterns were included. SCHEIN et al. [24] observed 22 percent CR in patients with PDL-D treated with CVP or MOPP, with a 14 month median survival. MCKELVEY et al. [22], reporting the studies of the Southwest Oncology Group with CHOP (cyclophosphamide, Adriamycin, Oncovin®, prednisone) and HOP (Adriamycin, vincristine, prednisone) observed that 50 to 71 percent of patients with MC-D or PDL-D achieved a CR and 75 percent of these patients were alive at three years follow-up. SKARIN et al. [26] reported an 80 percent CR rate

for patients with advanced PDL-D when treated with BACOP (bleomycin, Adriamycin, cyclophosphamide, Oncovin®, prednisone) and projected a 20 month disease-free survival of 75 percent. In the patients with advanced MC-D or PDL-D disease reported by BITRAN et al. [3] (Table II), an 82 percent CR rate was observed with COPP or COPA and an actuarial survival of 60 percent at 4 years was determined. Combination chemotherapy has thus significantly increased the survival of patients with MC or PDL diffuse disease. Furthermore, MCKELVEY [22] has noted a steeper remission duration curve in patients with PDL-D than patients with PDL-N. A higher relapse rate early in the course of therapy accounts for such an observation. Perhaps of more significance is a tendency of the remission duration curve to plateau in patients with PDL-D. This may be a sign of cure in some of these patients. In contrast, the CR duration curve for patients with PDL-N is linear, despite the fact that nodularity implies a more favorable responsiveness to chemotherapy. Intensive and aggressive chemotherapy is required in patients with MC or PDL diffuse disease if survival is to be substantially prolonged. Remission duration curves suggest that such chemotherapy is reducing the tumor burden to curable levels in a few patients.

The management of diffuse histiocytic lymphoma (HL-D) has been advanced considerably over the last 5 to 7 years. Patients with HL-D usually present with advanced disease, although a significant number may be in pathologic stage I or II on presentation [4]. Early combination chemotherapy for HL-D usually included cyclophosphamide, vincristine and prednisone (Table III). The complete response rates in these early studies increased from 5 percent to 30 to 60 percent but median survival was not significantly increased. LEVITT et al.[17], in 1972, reported a high rate of complete responders in a series of patients with advanced "reticulum cell sarcoma" treated with COMA, a program of combination sequential chemotherapy consisting of high-dose cyclophosphamide,

Oncovin®, methotrexate with leucovorin rescue, and cytosine arabinoside. Upon reclassification of the original biopsies by the Rappaport system, six of eight patients with HL-D were noted to have achieved a CR; five of these six patients have remained disease-free from 49 to 59 months [2]. The COMA program was patterned after data which suggested kinetic similarity between the L1210 mouse leukemia model and "reticulum cell sarcoma", as well as the fact that improved survival rates were observed in the L1210 model with a sequential form of chemotherapy that included cyclophosphamide, methotrexate and cytosine arabinoside. SWEET et al. reported similar results [32]. Combining the series from Yale and the University of Chicago permits study of 45 patients with HL-D treated with COMLA (L is leucovorin) and reveals a CR rate of 58 percent with disease-free remissions of more than 6 years [31]. Similar results have been achieved with C-MOPP (cyclophosphamide, Oncovin®, procarbazine, prednisone) [8] and BCOP (BCNU, cyclophosphamide, Oncovin®, prednisone) [11]. Recent reports now demonstrate the efficiency of combination chemotherapy which incorporates antitumor agents recently added to the chemotherapists' armamentarium, such as bleomycin and the anthracycline antibiotic, Adriamycin (doxorubicin hydrochloride). Furthermore, synergism has been demonstrated experimentally for Adriamycin and cyclophosphamide [7]. The Southwest Oncology Group reported CR rates of 68 percent and 66 percent in patients with advanced HL-D treated with CHOP or HOP respectively [21]. SCHEIN et al. reported on the successful NCI experience with BACOP [25]. Approximately 50 percent of previously untreated patients achieved a CR as defined by rigorous restaging criteria; the median duration of remission now exceeds one year. The three most successful programs for advanced HL-D, COMLA, CHOP (or HOP), and BACOP, incorporate an intensive induction phase, using very high dose cyclophosphamide (COMLA) or high dose cyclophosphamide plus Adriamycin. Tumor sensitivity and a relatively high log kill number must

account for part of the success of these programs. The COMLA program incorporates an 8-week cytoreductive phase using methotrexate and cytosine arabinoside, while the BACOP regimen uses bleomycin and prednisone in a similar manner. The CHOP/HOP program is one of repeated induction pulses. Not only are high CR rates achieved but long term, unmaintained median disease-free survivals are observed, ranging from 12 to 36 months. These patients have had their tumor burden reduced to a very few malignant cells and may be cured of their disease. One is not surprised: HL-D has an approximate doubling time of 17 days (range 12 to 23 days) [27]. The effectiveness of high dose cell cycle active agents is greater in tumors with high growth fractions.

Of recent concern has been the development of central nervous system (CNS) involvement by patients with HL-D, especially those patients with bone marrow involvement [6, 26]. The development of CNS disease as the only site of relapse in patients in remission is reminiscent of the pattern of relapse in children with acute lymphoblastic leukemia. Interestingly, in 50 patients with HL-D treated at the University of Chicago with either radiotherapy alone for pathologic stage I or II disease, or COMLA for advanced disease, no CNS disease has been observed, with follow-up as long as 65 months. MCKELVEY has also noted the rarity of CNS relapses in patients with HL-D maintained with OAP (Oncovin®, cytosine arabinoside, prednisone) versus those maintained with COP [20]. Programs reporting high CNS relapses have employed BACOP, MOPP, C-MOPP, or CHOP for induction therapy. The difference in these results may be due to the cure with radiotherapy alone in those patients with localized disease, and the use of COMLA in patients with advanced disease. Both methotrexate and cytosine arabinoside penetrate the blood brain barrier [12, 29]. These agents are given for eight consecutive weeks in each of 3 cycles, and may provide adequate sterilization for an existing low tumor burden. The

continuous long-term induction and consolidation nature of the COMLA regimen may prevent or cure seeding of the CNS by HL-D. Systemically administered cytosine arabinoside is efficacious in mice with intracranially transplanted L1210 tumors [16].

Careful pathologic staging (PS) may identify important subgroups of patients with diffuse histiocytic lymphoma. BITRAN et al. [4] has demonstrated that patients in PS I and perhaps PS II should receive radiation therapy with 5000 to 5500 rads. Perhaps more than 75 percent of these patients are cured. Selected patients with PS II disease, usually with bulky disease, may require radiation therapy and chemotherapy.

SUMMARY

Patients with malignant lymphoma, diffuse type, have an unfavorable prognosis when compared to those patients with nodular patterns. Prior to the introduction of combination chemotherapy, 50 percent survival rates for MC-D or PDL-D were about 2 years; HL-D, about 1 year. Aggressive combination chemotherapy for advanced MC-D or PDL-D results in complete remission rates of 22 to 82 percent, with median survivals of 1 to 2 years. Patients with localized diffuse histiocytic lymphoma are probably curable with radiotherapy alone in 75 percent of cases. Patients with advanced disease are best treated with intensive combination chemotherapy, achieving a long lasting complete remission in over one-half of cases, with median survivals now at 1 to 3 years. Many of these patients are probably cured; central nervous system relapse may now be a concern. The results of treatment of advanced histiocytic lymphoma are now approaching the results reported for advanced Hodgkin disease.

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TABLE I. Fifty percent survival in years for previously untreated patients with non-Hodgkin lymphomas

Author, Reference [ ] (Number of patients)	Nodular		Diffuse	
	MC/PDL	HL	MC/PDL	HL
JONES et al. [14] (405)	8 - 9*	4	2	1
DUMONT et al. [10] (244)	>5 >5	-	1	1
BROWN et al. [5] (460)	>5 >5	4	1.5 - 2.5	1

*Acturial

See text for abbreviations.

TABLE II. Response to combination chemotherapy in patients with advanced MC or PDL lymphoma

Author Reference [ ]		Treatment†	Year	Complete Remission (Percent)
HOOGSTRATEN et al.	[13]	COP	1969	35
LOWENBRAUN et al.	[18]	MOPP	1970	48
LUCE et al.	[19]	COP	1971	50
BAGLEY et al.	[1]	CVP	1972	57
STEIN et al.	[30]	COPP	1974	58
SCHEIN et al.*	[24]	CVP/MOPP	1974	22
McKELVEY et al.*	[21]	CHOP	1976	69
		HOP	1976	54
SKARIN et al.*	[26]	BACOP	1977	80
BITRAN et al.*	[3]	COPP/COPA	1977	82

*Series does not include nodular types.

†See text for abbreviations

TABLE III. Response to combination chemotherapy in patients with advanced diffuse histiocytic lymphoma

Author Reference [ ]		Treatment*	Year	Complete Remission (Percent)
HOOGSTRATEN et al.	[13]	COP	1969	31
LOWENBRAUN et al.	[18]	MOPP	1970	38
LUCE et al.	[19]	COP	1971	39
LEVITT et al.	[17]	COMA	1972	75
DeVITA et al.	[8]	C-MOPP	1975	41
BERD et al.	[2]	COMA	1975	60
DURANT et al.	[11]	B-COP	1975	50
SWEET et al.	[32]	COMA	1976	77
McKELVEY et al.	[21]	CHOP	1976	68
		HOP	1976	66
SCHEIN et al.	[25]	BACOP	1976	50
SWEET et al.	[31]	COMLA	1977	68

*See text for abbreviations

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