213 Low-dose metronomic scheduling of chemotherapy for advanced stage III-IV non-Hodgkin lymphoma: An observational study from a single center with a 25-year minimal follow-up.

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Introduction

Although conventionally scheduled chemotherapy (CCT) to the management of advanced/relapsed indolent non-Hodgkin lymphoma (ARINHL) produce high response rates they do not prolong survival, and they are rarely curative. The clinical course of ARINHL is characterized by unpredictable clinical aggressiveness, multiple relapses, shorter duration of response to re-treatment, transformation to a more malignant phenotype, and resistance to conventional anthracycline-based chemotherapy [1]. Also, intensive and myeloablative therapy with bone marrow rescue and immunological therapy with anti-CD 20 monoclonal antibodies have been proposed, but there is no evidence that survival has been improved [2]. The experience that re-treatment with CCT can seriously impair the quality of life led us to choose a nonstandard low-dose chemotherapy (NCT) administered weekly/bi-weekly enabling maintenance of the palliative therapy in patients (pts) not suitable for the CCT.

Patients and methods

The study population included 109 treatment requiring pts with ARINHL referred to the Department of Oncology between May 1, 1975 and December 1, 1981. Inclusion criteria were: histopathologically proven disease according to the Kiel classification, measurable/evaluable disease, performance status <4 WHO and informed consent. CLL and plasma cell malignancies were excluded. There were 61 men and 48 women, median age 61 years, range 27-84. Centrocytic diffuse types were presented in 65 and centroblastic/centrocytic nodular or nodular+diffuse in 44 pts, respectively. The characteristics are listed in Table 1.

Table 1 CR rates by chemotherapy regimens in ARINHL

Type of chemotherapy	No. of (%)					
	Regimens		CR			95% CI
Conventional CCT						
CVP	52		14 (27)			
CHOP	31	99	8 (26)		28 (28)	20-38
PmM	16		6 (38)			
Other*	30		8 (27)		8 (27)	8-39
Total	129		36 (28)			
Nonstandard NCT						
VADRIAC	34		19 (56)			
PRM	30	91	18 (60)		54 (59)	49-70
CV(P)	27		17 (63)			
Other**	79		18 (23)		18 (23)	14-34
Total	170		72 (42)			
Total No of regimens	**299**		**108 (36)**			

Chemotherapy

CVP, CHOP, other combinations, oral chlorambucil/trophosphamide was delivered to the pts eligible for CCT. The NCT was chosen for pts not eligible for CCT. The combination chemotherapy such as MACOP-B, VACOP-B, BACOP, ChlVPP, MIME, MOPP administered weekly/biweekly were not generally recognized as a standard treatment for indolent NHL. Dyxirazine 20 mg i.v. or prochlorperazine, 25 mg suppository, before and after administration of the i.v. chemotherapy, were used to reduce nausea. A hydrocortisone i.v. bolus was given occasionally in the CCT to support the antiemetic medication otherwise corticosteroids were avoided in NCT regimens. Pts achieving complete remission (CR) were encouraged to obtain additional courses for consolidation provided that the response during the final treatment lasted for a minimum of one month. This extended treatment was given to 34 pts. The chemotherapy schedules are shown in Table 2. As the front-line therapy 58 pts (53%) received the CCT and 51 pts (47%) the NCT. In the final treatment 37 pts (34%) received the CCT and 72 (66%) the NCT. Of a total of 299 regimens used, 129 were CCT and 170 NCT. Because of a precise evaluation of partial remission may be difficult in ARINHL, we defined CR and non-CR only in our evaluation of response. Localized relapses were treated with involved field radiotherapy. Pts were only re-treated when there was evidence of disease progression. CVP or CHOP as a second line therapy were only given to pts with normal blood cell counts and expected good tolerance to CCT. Generally, management in second and subsequent relapses was the same as for the first. Inspired by toxicological studies in chemotherapy [3], we invented the Rate of Administered Dose of Cytostatic (RADOC) according to the formula: total dose of cytostatic (mg) divided by duration of treatment (no. of weeks). The higher rate=the higher dose per fraction and more pronounced toxicity.

Results

The median number of relapses was three, ranging from one to eight. Recurrences occurred frequently in 59% of pts during the first two years and decreased to 33% during the years 3-10. The minimum of follow-up was 25 years and the maximum almost 31 years. There were two pts who relapsed after 10 years and two after 22 years, respectively. One patient relapsed 23 years, being symptom-free after the last NCT. Median time to relapse was four months in the CCT group, range 0.5-144, and 25 months in the NCT group, range 2-278, respectively, $p<0.001$. The results of treatment favored pts treated according to the NCT schedules as seen in Table 3 and 4. The RADOC was significantly lower for both CTX and ADM in the NCT when compared with the conventionally treated CCT group using the same agents. Distribution of toxicity is seen in Table 5. The overall survival proportion was 64% at 10-, 16% at 20-, and 9% at 25-year follow-up, respectively. The cause-specific survival, taking into account deaths due to lymphoma only, was 38%.

Discussion

Folkman [4], Kerbel and Kamen [5] have found evidence that tumors are angiogenesis dependent, and a new modality, antiagiogenetic treatment is now moving in to clinical trials. Recently, Burton and co-workers [6] have demonstrated the benefit of the weekly scheduling of chemotherapy in elderly patients with aggressive NHL in a phase III trial. Presently, we cannot decide the exact mechanism by which NCT reduced lymphoma progression, but this retrospective study suggests that the low-dose metronomic scheduling of chemotherapy may be a breakthrough treatment in pts with ARINHL, achieving significantly higher rate of sustainable remissions, frequent re-induction of remission at relapse, low toxicity and good tolerance.

References

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