Cancer Chemother Pharmacol (1991) 29: 80–82

Cancer Chemotherapy and Pharmacology

Short communication

Intensive chemotherapy for adult lymphoblastic lymphomas

Raymond Liang[1], David Todd[1], T. K. Chan[1], Edmond Chiu[1], Albert Lie[1], Faith C. S. Ho[2], and S. L. Loke[2]

Department of [1] Medicine and [2] Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong

Received 5 April 1991/Accepted 25 June 1991

Summary. A total of 20 adults patients presenting with previously untreated lymphoblastic lymphoma underwent an intensive chemotherapy protocol. Either the BACOP or the m-BACOD regimen was used for induction. If the patients achieved a complete clinical remission (CR) after three courses, they were given intensive consolidation and maintenance chemotherapy based on a protocol that was modified from the L10/L17M regimen of the Memorial Sloan-Kettering group for acute lymphoblastic leukaemia and lymphoblastic lymphoma. Patients exhibiting localised areas of bulky disease were given additional involved-field ratiotherapy. In all, 15 (75%) men and 5 (25%) women were entered in this study. Their median age was 28 years (mean, 30 years; range, 12–64 years). Overall, 3 (15%) had stage II disease, 3 (15%) had stage III disease and 14 (70%) had stage IV disease; 7 (35%) patients exhibited B symptoms and 4 (20%) had bulky disease. The overall (CR) rate was 10/20 (20%), and that following BACOP and m-BACOD therapy was 4/8 (50%) and 6/12 (50%), respectively. In all, 7 of the 10 complete responders (70%) relapsed. The disease-free survival of the ten who achieved a CR was 23% at 3 years. The overall survival of all 20 patients at 3 years was only 37%, and there were very few long-term survivors. More effective treatment for adult lymphoblastic lymphoma is required.

Introduction

Lymphoblastic lymphoma is characterised by the aggressiveness of its course and patients who suffer from the disease usually exhibit poor long-term survival [3, 5, 9, 10, 14]. Although they are often treated in the same way as are individuals who display intermediate-grade lymphomas, their clinical outcome is generally poorer [8]. Clinical studies have shown that more intensive therapy may improve their prognosis [3, 14]. Chemotherapeutic regimens originally designed to treat lymphoblastic leukaemia have been used for lymphoblastic lymphoma and have achieved good results [14]. In this report we describe the clinical outcome of 20 patients presenting with lymphoblastic lymphomas who underwent an intensive chemotherapy protocol.

Offprint requests to: Raymond Liang, University Department of Medicine, Queen Mary Hospital, Pokfulam, Hong Kong

Patients and methods

From January 1984 to December 1990, 20 patients presenting with previously untreated lymphoblastic lymphoma at the University Department of Medicine, Queen Mary Hospital, Hong Kong, were treated with intensive chemotherapy. Prior to July 1986, the BACOP regimen was used for induction [12]. An attempt was made to improve the treatment results after July 1986 by using the m-BACOD regimen instead [13]. If the patients achieved a complete clinical remission after three courses, they underwent an intensive consolidation and maintenance chemotherapy protocol plus central nervous system prophylaxis as modified from the L10/L17M regimen of the Memorial Sloan-Kettering group for acute lymphoblastic leukaemia and lymphoblastic lymphoma [14]. Patients displaying localised areas of bulky disease were given additional involved-field radiotherapy.

The pathological materials were classified according to the Working Formulation [10]. When fresh tissue specimens were available, immunohistochemical studies were performed using the immunoperoxidase technique [4]. A panel of commercially available monoclonal antibodies was used.

All patients were staged according to the Ann Arbor system [2]. Clinical staging procedures included a complete history and physical examination, a chest radiograph, full blood counts, blood biochemistry, a bilateral iliac-crest trephine biopsy and an aspirate of bone marrow. Computerised axial tomography was performed to exclude abdominal lesions. Barium studies and/or endscopic examinations were done when gastrointestinal involvement was clinically suspected. Laparotomy was not routinely carried out.

Tumour response was assessed using standard criteria [6]. The Kaplan-Meier product-limit method was used to generate disease-free survival (DFS) and overall survival curves [7]. DFS was measured from the date of first remission to the date of first relapse. The overall survival was measured from the date of diagnosis to the date of death or last follow-up. The log-rank procedure was used to compare the survival curves and the chi-square test with Yates' correction was used to compare complete response (CR) and relapse rates.

Results

A total of 20 patients suffering from lymphoblastic lymphomas were investigated, including 15 (75%) men and 5 (25%) women. The median age was 28 years (mean, 30 years; range, 12–64 years). In all, 3 subjects (15%) had stage II disease, 3 (15%) had stage III disease and 14 (70%) had stage IV disease; 7 (35%) patients exhibited B symptoms and 4 (20%) had bulky disease. The disease involved the lymph nodes in all 20 (100%) subjects (mediastinal in 13 cases), bone marrow in 13 (65%), the liver in 9 (45%), the spleen in 8 (40%), pleura in 6 (30%), the pericardium in 2 (10%), subcutaneous soft tissue in 2 (10%), skin in 1 (5%), Waldeyer's ring in 1 (5%) and the stomach in 1 (5%). The mean serum lactate dehydrogenase level was 576 μmol min^{-1} l (range, 277–3,445 μmol min^{-1} l; normal, <350 μmol min^{-1} l) and the mean serum albumen level was 35 g/l (range, 19–50 g/l). Fresh tissue specimens were available from ten patients, and all exibited the T-immunophenotype.

The induction chemotherapy consisted of BACOP in 8 patients and m-BACOD in 12. Subjects who achieved a CR after three courses underwent the consolidation and maintenance chemotherapy protocol. In all, 8 (40%) patients received additional local radiotherapy to areas of bulky disease.

The overall CR rate was 10/20 (50%), and that following BACOP and m-BACOD therapy was 4/8 (50%) and 6/12 (50%), respectively. In all, 7 of the 10 complete responders (70%) relapsed. The DFS of the ten patients who achieved a CR was 23% at 3 years. Fig. 1 shows the DFS curve for the 10 complete responders and the overall survival curve for all 20 patients. The overall survival of all patients at 3 years was only 37%. Because of the small number of patients investigated in this study, factors including the induction regimen (BACOP or m-BACOD), sex, age, B symptoms, the presence of bulky disease, the primary site of disease, serum lactate dehydrogenase levels, serum albumen levels and the clinical stage did not appear to predict the clinical outcome.

Myelosuppression was the major toxicity. In all, 7 (35%) patients experienced one or more episodes of neutropenic infections, including septicaemia and pneumonia, which were fatal in 1 case; 3 (15%) subjects developed serious but nonfatal gastrointestinal bleeding as a complication of thrombocytopenia. All patients exhibited alopecia and experienced nausea and vomiting. One 40-year-old patient developed secondary myelodysplastic syndrome at 33 months after the commencement of chemotherapy, and it subsequently progressed to acute myeloid leukaemia.

Discussion

The prognosis of lymphoblastic lymphoma is generally poor [3, 5, 9, 14]. Combination chemotherapy regimens such as CHOP (consisting of cyclophosphamide, doxorubicin, vincristine and prednisone) induce a CR in >50% of patients exhibiting intermediate-grade lymphoma and result in long-term DFS in at least one-third of these subjects

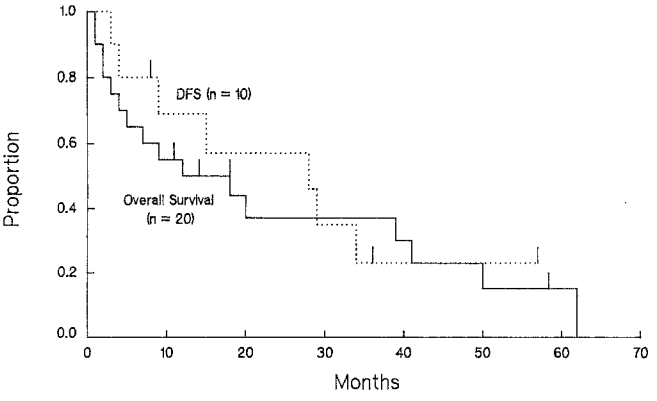

Fig. 1. The disease-free survival of the 10 patients who achieved a CR and the overall survival of all 20 patients suffering from lymphoblastic lymphoma

[8]. Although similar regimens have also been used for lymphoblastic lymphoma, the clinical outcome has been less satisfactory.

The best management of lymphoblastic lymphoma remains uncertain. However, there is evidence suggesting that more intensive chemotherapy may improve the prognosis of this disease [3, 14]. In the present study, patients received one of the two different induction regimes, BACOP or m-BACOD. In our previous experience with these two regimens in patients exhibiting advanced intermediate- and high-grade non-Hodgkin's lymphomas, no significant difference was found in their efficacy [8]. In the present study, the two regimens produced similar CR rates; thus the results were grouped together for analysis. The overall CR rate of 50% is comparable to the results of other clinical studies using similar induction regimens for the treatment of intermediate- and high-grade non-Hodgkin's lymphomas [8].

It has been noted that lymphoblastic lymphoma is associated with a high relapse rate and short DFS even after a CR has been achieved [14]. Therefore, the L10/L17M consolidation and maintenance protocol, which has been shown to be effective in preventing relapses in patients presenting with acute lymphoblastic leukaemia and lymphoblastic lymphoma, was used in the present study. Nevertheless, a high relapse rate of 70% was observed after the completion of treatment. The overall survival of these patients remained poor and long-term survivors were uncommon (Fig. 1).

More effective treatment for adult lymphoblastic lymphoma is needed. The results of autologous or allogeneic marrow transplantation (BMT) for lymphoblastic lymphoma appear to be encouraging [1]. Most patients exhibiting lymphoma who have undergone BMT have previously experienced a relapse or have displayed initially refractory disease. It appears that those who have experienced a chemotherapy-sensitive relapse fare better following than to those who exhibit chemotherapy-resistant disease. As the initially good response following conventional chemotherapy for lymphoblastic lymphoma often leads to eventual relapse, BMT has been used as a kind of intensive consolidation therapy and has achieved good results [1, 11].

References

1. Armitage JO (1989) Bone marrow transplantation in the treatment of patients with lymphoma. Blood 73: 1749–1758
2. Carbone PP, Kaplan HS, Mushoff K, Smithier DW, Tubiana M (1971) Report of the committee on Hodgkin's disease staging. Cancer Res 31: 1860–1861
3. Coleman CN, Pocozzi VJ, Cox RS, McWhirter K, Weis LM, Cohen JR, Yu KP, Rosenburg SA (1986) Treatment of lymphoblastic lymphoma in adults. J Clin Oncol 4: 1628–1637
4. Ho FCS, Loke SL, Hui PK, Todd D (1986) Immunohistological subtypes of non-Hodgkin's lymphoma in Hong Kong Chinese. Pathology 18: 426–430
5. Hollema H, Poppema S (1989) T-lymphoblastic and peripheral T-cell lymphomas in the northern part of the Netherlands, an immunologic study of 29 cases. Cancer 64: 1620–1628
6. Hoogstraten B (1984) Reporting treatment results in solid tumour. In: Buyse ME, Staquet MJ, Sylvester RJ (eds) Cancer clinical trials, methods and practice. Oxford University Press, Oxford, pp 139–156
7. Kaplan EL, Meier P (1958) Non-parametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481
8. Liang R, Chiu EKW, Chan TK, Todd D, Loke SL (1990) Management of advanced stage intermediate grade non-Hodgkin's lymphomas. Hematol Oncol 8: 147–154
9. Liang R, Loke SL, Ho FCS, Chiu E, Chan TK, Todd D (1990) Histological subtypes and survival of Chinese patients with non-Hodgkin's lymphomas. Cancer 66: 1850–1855
10. Non-Hodgkin's Lymphoma Pathologic Classification Project (1982) National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a Working Formulation for clinical usage. Cancer 49: 2112–2135
11. Santini G, Coser P, Chisesi T, Porcelini A, Sertoli R, Contu A, Vinante O, Congiu AM, Carella AM, D'Amico T, Pierluigi D, Rossi E, Scarpati D, Rizzoli V (1991) Autologous bone marrow transplantation for advanced stage adult lymphoblastic lymphoma in first complete remission. Ann Oncol 2 [Suppl]: 181–185
12. Schein PS, De Vita VT Jr, Hubbard S, Chabner BA, Canellos GP, Berard C, Young RC (1976): Bleomycin, Adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) combination chemotherapy in the treatment of advanced aggressive histiocytic lymphoma. Ann Intern Med 85: 417–422
13. Shipp MA, Harrington DP, Klatt MM, Jochelson MS, Pinkus GS, Marshall JL, Rosenthal DS, Skarin AT, Canellos GP (1986) Identification of major prognostic subgroups of patients with large cell lymphoma treated with m-BACOD or M-BARCOD. Ann Intern Med 104: 757–765
14. Slater DE, Mertelsmann R, Koziner B, Higgins C, McKenzie S, Schauer P, Gee T, Straus D, Kempin S, Arlin Z, Clarkson BD (1986) Lymphoblastic lymphoma in adults. J Clin Oncol 4: 57–67