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Short communication

Non-aggressive therapy for chronic myeloid leukaemia in blastic transformation

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Summary. A total of 40 patients presenting with chronic myeloid leukaemia in blastic transformation were treated with a non-aggressive chemotherapy regimen consisting of vincristine, cytosine arabinoside and thioguanine. Remissions were achieved by 3/10 (30%) patients displaying lymphoid transformation (remission duration, 2, 3, and 5 months, respectively) and by 5/30 (17%) subjects exhibiting myeloid changes (duration 2+, 4, 4, 5 and 7 months, respectively). Myelosuppression was the major toxicity and non-haematological toxicities were mild and acceptable. The median survival of patients exhibiting lymphoid and myeloid blastic transformation as measured from the time of transformation was 6 and 3 months, respectively, but the difference was not statistically significant. Three subjects displaying lymphoid transformation and five showing myeloid changes survived for >12 months after the time of transformation.

Introduction

Blastic transformation is the major cause of mortality in patients presenting with chronic myeloid leukaemia (CML). Although the chronic phase of CML is easy to control with busulphan or hydroxyurea, these agents do not prevent blastic transformation and thus cannot effect a cure. The intensive chemotherapy regimens that are useful in treating acute leukaemia are generally much less effective in cases of CML in blastic transformation [6]. This report describes the follow-up data obtained for 85 Hong Kong Chinese patients presenting with CML. The time to blastic transformation was estimated and the results obtained using a non-aggressive therapy protocol for those in blastic transformation were studied.

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Patients and methods

Between January 1980 and June 1990, 85 patients presenting with CML in the chronic phase were seen in the University Department of Medicine, Queen Mary Hospital, Hong Kong. Pretreatment assessment included a history and physical examination, complete blood counts, blood biochemistry, a peripheral blood and marrow examination, a cytogenetics study on the marrow specimen, determination of the neutrophil alkaline phosphatase score and a chest radiograph. Subjects were treated with either busulphan or hydroxyurea. Allopurinol together with adequate hydration was also given on the detection of high white cell counts. In all, 12 CML patients exhibiting de novo blastic transformation at the time of presentation were excluded from this analysis.

Bone marrow examination was repeated when clinical features suggesting blastic transformation appeared, such as systemic symptoms, increasing splenomegaly, extramedullary involvements, anaemia, thrombocytopenia or increasing peripheral blast counts. The type of transformation (lymphoid or myeloid) was determined by morphological and cytochemical investigations. In selected cases, immunophenotyping was also performed by the immunoperoxidase technique using a panel of commercially available monoclonal antibodies [8].

By the time of this analysis, 46 cases of CML had transformed to acute leukaemia, which was defined as the presence of >30% blast cells in the bone marrow [5–7]. Of these patients 40 received 2 mg vincristine weekly for 2–4 weeks followed by 100 mg/m^2 cytosine arabinoside given daily by intravenous infusion over 18 h plus 100 mg/m^2 oral thioguanine given daily for 5–10 days; this regimen was given every 4–8 weeks. Hydroxyurea was given concomitantly, its dose being titrated according to the total white cell count. The other six patients received more intensive treatment that contained daunorubicin or doxorubicin. Subjects exhibiting disease in the accelerated phase (marrow blast count, 5%–30%) were not included in this study until their marrow blast counts had reached a value of >30%. Central nervous system (CNS) prophylaxis was not routinely given. Six patients who developed CNS involvement subsequently received intrathecal methotrexate and/or cranial irradiation.

A clinical remission was defined as a reversion to the chronic phase as shown by the presence of <5% blasts in the bone marrow. The Kaplan-Meier product-limit method was used to estimate both the time to transformation and the survival following blastic transformation.

Results

A total of 85 CML patients were included in this analysis, of which 53 (62%) were men and 32 (38%) were women.

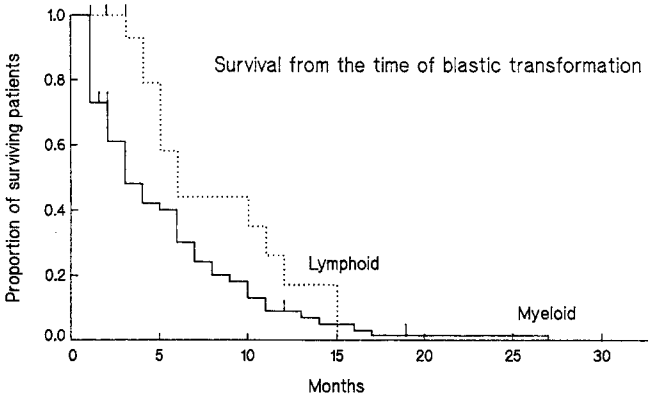

Fig. 1. The survival of 40 patients exhibiting CML blastic transformation

Their median age was 42 years (range, 12–80 years). In all, 76 (89%) subjects had palpable splenomegaly measuring from 1 to 28 cm (median, 14 cm). The initial white cell and platelet counts ranged from 27 to 467 and from 85 to 1856 10^9/l, respectively. The neutrophil alkaline phosphatase score was determined in 60 patients and amounted to <20 in 56 cases. The cytogenetics study was successful in 69 patients, among whom the Philadelphia chromosome was detectable in 62 cases (90%). In all, 65 (76%) subjects received hydroxyurea and 20 (24%) were given busulphan during the chronic phase.

By the time of this analysis, 46 cases had transformed to acute leukaemia, the median time to transformation being 44 months. Of these patients, 40 were treated with a non-aggressive chemotherapy regimen consisting of vincristine, cytosine arabinoside and thioguanine. This group included 25 (63%) men and 15 (37%) women aged a median of 45 years (range, 15–68 years). The percentage of blast cells in marrow ranged from 35%–95%. In all, 10 (25%) of them exhibited lymphoid transformation and 30 (75%), myeloid changes. Remissions were achieved by 3 (30%) patients showing lymphoid transformation (remission duration, 2, 3 and 5 months, respectively) and by 5 (17%) displaying myeloid transformation (duration, 2+, 4, 4, 5 and 7 months, respectively). Myelosuppression was the major toxicity and non-haematological toxicities, including nausea and vomiting, mucositis and neuropathy, were mild and acceptable. The median survival of patients exhibiting lymphoid and myeloid blastic transformation as measured from the time of transformation was 6 and 3 months, respectively, but the difference was not statistically significant (Fig. 1). Three subjects displaying lymphoid transformation and five showing myeloid changes survived for >12 months after the time of transformation.

Discussion

CML in blastic transformation is generally associated with a very poor prognosis, the median survival usually being only a few months. There has thus far been no evidence that intensive chemotherapy as used in acute leukaemia can improve the survival of these patients [1–7, 9–12]. The remission rates achieved using these intensive treatment regimens remain low and the remissions are usually of very brief duration. These individuals also tolerate intensive treatment poorly, often developing severe toxicities and prolonged marrow aplasia. A recent analysis of 242 patients presenting with CML in blastic crisis revealed that the overall median survival as measured from the time of blastic crisis was only 18 weeks; complete remission could be achieved by only 23% of these subjects [5].

In recent years we have adopted a non-aggressive approach for the treatment of these patients. Vincristine alone was used initially and was followed by a combination of cytosine arabinoside and thioguanine. Excessively high white cell counts were controlled by the continuous administration of hydroxyurea, the dose of which was titrated according to the white cell counts. Remissions were achieved by 20% of our patients. The treatment was usually well tolerated by our subjects, who were managed as outpatients until the disease had become resistant to therapy. As compared with reports in the literature, the overall survival of our patients was similar to that of subjects receiving more intensive therapy.

This non-aggressive approach has the advantage of avoiding the early morbidity and mortality that are associated with the toxicities produced by intensive treatment. Although only a small proportion of our patients achieved a remission, which was often of brief duration, 8 of 40 (20%) subjects managed to survive for >12 months. As in the other reports in the literature [3, 5], our patients exhibiting lymphoid transformation generally responded better and survived longer than those displaying myeloid changes, but the differences were not statistically significant. It has also been found that CML in blastic transformation is associated with a high incidence of mixed lineage expression at the microscopic, ultrastructural, cytochemical, immunophenotypic and molecular levels [8].

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