Growth Factors in Elderly Patients with Acute Myeloid Leukemia

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Abstract. AML disease in elderly patients is a frequent and severe disease with a high early death rate, low complete remission rate, and short median survival. By reducing the intensity of the induction treatment the complete remission was reduced. The proposal is to give an intensive chemotherapy to elderly patients in order to have a high complete remission rate associated with a drug which potentially minimizes the early mortality. Since the early promising reports, several large prospective, randomized controlled trials have assessed the efficacy of G-CSF in elderly patients. No significant induction of leukemia regrowth was observed in the various trials with either G-CSF or GM-CSF. No clear reduction in chemotherapy related mortality was observed. CSFs increase the complete remission rate after intensive induction treatment in patients with poor prognosis factors mainly patients with persistent blast infiltration in bone marrow after induction treatment. CSFs could also improve the survival time in some cases, mainly in the younger population of elderly persons.

Introduction

Acute myeloid leukemia (AML) in the elderly is a frequent disease. More than 40% of patients with AML are over 65 years old at the time of diagnosis [1, 2]. AML disease in elderly patients often has poor prognostic factors such as involvement of immature progenitor cells [3] or myelodysplastic features or a prior myelodysplastic syndrome [4, 5], and particular chromosomal abnormalities [6, 7, 8] such as monosomy 7 or the loss of the long arm of chromosome 5.

The mortality rate during induction therapy increases with age. For patients over 55 to 60 years of age, the treatment related early death rate is in the range of 25 to 40% [9, 10, 11, 12].

If complete remission is achieved in more than 75% of adults less than 60 years old, only about 45% of elderly patients receiving similar treatment have a complete remission [13, 14, 15]. In the AML 8 trial in UK [13] the complete remission rate is directly related to the age (70% before 60 years old, 52% between 60-69 years old, and 26% after 70 years old).

The median survival, even after complete remission, still remains relatively short between 9 to 12 months, in elderly AML patients [10, 12, 16], although a relatively low median age of enrolled patients (≤ 70 years).

From these poor results, high early death rate, low complete remission rate, short median survival, several approaches were attempted to improve the outcome of the acute myeloid leukemia in elderly patients.
Is It Possible to Reduce Early Mortality by Reducing the Intensity of the Induction Treatment?

A multicentric randomized trial was conducted comparing low dose Cytosine Arabinoside (LD Ara-C) to conventional chemotherapy (Daunorubicin and Cytosine Arabinoside) [15] in order to reduce the early mortality. The early death rate was 10% in patients treated by LD Ara-C, compared to 32% in patients treated by conventional chemotherapy. The number of transfusions, days of hospitalisation and the antibiotic requirements were reduced in patients treated by LD Ara-C. The median survival was similar in both population. Thus the early mortality rate is reduced while simultaneously the complete remission was also reduced.

Are the Growth Factors Able to Reduce the Early Mortality Rate?

The proposal is to give an intensive chemotherapy to elderly patients in order to have a high complete remission rate, associated with a drug which potentially minimizes the early mortality. Infections cause approximately two third of treatment associated deaths [17, 18, 19]. The use of myeloid CSFs could decrease the time of neutropenia and thus the number of infections. However the potential for in vitro cytokine stimulation of leukemia cells has reduced the enthusiasm in conducting trials with colony stimulating factors.

The first trial was conducted by Buchner et al. [20, 21]. GM-CSF was administered in 30 elderly or relapsed AML patients with an aplastic bone marrow after the completion of chemotherapy. A historical control group of similar patients who had not received GM-CSF was used for comparison. The duration of neutropenia was reduced by 6 to 9 days in patients treated with GM-CSF. The early death rate was significantly reduced (14 vs. 39%) and there was a trend towards more complete remissions in the GM-CSF group (50 vs. 32%). Remission durations were identical in both groups. Two patients experienced marked leukemic regrowth with GM-CSF therapy; however, this was totally reversible in one of them once GM-CSF had been discontinued.

In 1990, Ohno et al. [22] published the results of the first Japanese randomized controlled study of G-CSF administered after the completion of induction chemotherapy in a heterogeneous population of patients with refractory or relapsed acute leukemia. Each patient received an individualized, response-oriented induction course of mitoxantrone, etoposide, and behenoylcytosine arabinoside. Mitoxantrone and occasionally etoposide doses were increased in cases of persistent blast cells in the bone marrow examination on Day 8, Day 10, and sometimes Day 12. Only patients achieving a severe bone marrow hypoplasia after chemotherapy were randomized to receive G-CSF or placebo. Even though patients treated with G-CSF received higher doses of chemotherapy than those treated with placebo, their neutrophil counts recovered significantly earlier to a level higher than 500/mm³ or 1000/mm³. The duration of neutropenia was decreased by about 1 week. The incidence of documented infections was significantly lower in the G-CSF group. There was no difference between the two treatment groups in terms of leukemia regrowth with G-CSF / placebo therapy. Furthermore, there was a trend towards a higher CR rate in the G-CSF group (50% compared to 36% in the placebo group). Remission durations were similar in both groups.

Since these early promising reports, several large prospective, randomized, controlled trials have assessed the efficacy of CSF (or GM and G-CSF) in elderly patients [23, 24, 25, 26, 27, 28]. No significant induction of leukemia regrowth was observed in the various trials with either G-CSF or GM-CSF.

Some investigators restricted CSF administration to patients with a documented aplastic bone marrow after the induction course, as used in early Japanese and German reports. In contrast, the growth factor was administered not only after the completion of chemotherapy, but also during and occasionally before the chemotherapy in some studies. The effects of CSF in the history of the disease are detailed in Tables 1, 2 and 3.