Review article

Treatment of acute leukemia

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Summary

Leukemic cells are highly sensitive to chemotherapeutic agents. A reduction of the leukemic burden is easily achieved by chemotherapy in most cases. However, it is difficult to reduce the number of leukemic cells to such an extent that a regrowth does not occur and the patient is cured.

Traditionally the therapy of acute leukemia is divided into induction and post remission therapy. The aim of the induction therapy is to reduce the number of leukemic cells to a morphologically undetectable level allowing normal hemopoiesis to recover. The goal of the post remission treatment is a further reduction of leukemic cells to zero or to very low levels which can be controlled by (still unknown) endogenous mechanisms. In some recent treatment protocols induction and the early part of post remission treatment are not strictly separated.

Treatment of acute myeloid leukemia (AML)

Induction therapy

The standard induction therapy which is commonly used in de novo AML (except M3) is the combination of daunorubicin (DNR) 45 mg/m² on days 1 to 3 and cytosine arabinoside (ARA-C) 100 mg/m²/d for seven days by continuous infusion (3+7 protocol) [1]. Many modifications of this original protocol have been tested. From these studies it appears to be established that a reduction of dose intensity (for example reduction of the DNR dose to 30 mg/m²/d) is associated with a lower response rate [2, 3]. Less clear is whether in younger patients an increase of dose intensity or a replacement of DNR by mitoxantrone, idarubicin or amsacrine improves the response rate. A meta-analysis of randomised trials [4] found a higher remission rate with idarubicin and mitoxantrone compared to various doses of DNR but no improved overall survival. Löwenberg et al. [5] compared DNR (30 mg/m² days 1–3) and mitoxantrone (8 mg/m² days 1–3) in older patients. The remission rate with mitoxantrone was higher, but this did not translate into an improved overall survival. The addition of etoposide to a standard induction protocol does not increase the remission rate and the long term outcome [6]. High dose ARA-C has been used in the induction in several uncontrolled and two randomised studies [7, 8]. In the randomised studies the remission rate was not higher, but the toxicity considerable. However, the long term outcome in the high dose group was better in one study [7]. It must be mentioned that in this study the standard dose group did not receive high dose ARA-C during consolidation.

A complete hematological remission (CR) can be achieved in 50%–80% of patients [9, 10]. The reasons for failure are death from infection, bleeding during induction therapy, or drug resistance. When G-CSF and GM-CSF became available it was hoped that the remission rate could be improved in two ways. Since it has been shown that these growth factors make leukemic cells more sensitive toward cytarabine they were administered before and during chemotherapy. While initial results appeared promising [11], randomised trials did not show an improved remission rate [12-14]. However, in one of these studies [14], the disease free survival was significantly longer in the GM-CSF group. Another approach was to administer G-CSF or GM-CSF after chemotherapy in order to shorten the time of neutropenia and thereby reduce the number of toxic deaths. While the earlier recovery of neutrophils (usually by five days) could be confirmed in all trials, this did not translate in fewer infections and an improved remission rate in most trials [9,15,16]. However, in a recent large trial [17] it could be shown that the duration of antibiotic treatment and the hospital stay could be significantly shortened by G-CSF. With one exception [18] all trials have shown that G- or GM-CSF can be safely given to patients with AML and there is no increased risk of resistance or recurrence. Recently, MGDF has been tested in AML [19]. When given after chemotherapy MGDF increased platelet counts in a dose dependent manner. However, there was no earlier recovery of platelets and as a consequence no reduction of the number of platelet concentrates required to keep the platelet count above 20,000.

The chance of CR depends on a number of leukemia and patient related factors. The most important prognostic factors are patient age and the karyotype of the leukemic cell [10]. While patients under the age of 60 have a remission chance of 70%–80%, the CR rate of patients over 60 years is only 50%–60% (Figure 1). The lower remission rate in older patients is due to a higher death rate during induction, but also to a greater number of resistant cases. Karyotype is an
important prognostic factor in all age groups (Table 1). The percentage of patients with unfavourable karyotype is higher in older patients which partly explains the poorer response to chemotherapy (Figure 2). Other prognostic factors are the performance status at diagnosis, high tumour burden and the presence of drug resistance proteins [20, 21].

In acute promyelocytic leukemia (APL) the treatment of choice is the combination of all trans retinoic acid (ATRA) and chemotherapy [22]. Currently several trials evaluate the optimal timing of ATRA and chemotherapy (simultaneous or sequential) and whether high doses of an idarubicin alone [23] are superior to the standard combination of anthracyclin and cytarabine. ATRA reverses rapidly the coagulopathy and prevents severe bleeding which was often the cause of death during chemotherapy. Remission rates exceeding 80%-90% have been reported in several trials [22, 23], but in older patients and in those with high leukocyte counts the treatment is less successful. Molecular remissions can be achieved in more than half of patients after one induction course and in more than 90% after consolidation therapy [23].

Special attention must be paid to the induction therapy in elderly patients since they are at a higher risk of toxic death during induction. The death rate may be lower when attenuated doses of chemotherapy are given. However, several trials have shown that the overall result is better when intensive chemotherapy is given [3, 5].

Patients who are refractory to two induction courses have a poor prognosis. However, about 15%-20% of younger patients can be cured by allogeneic bone marrow transplantation with a sibling or an unrelated matched donor [24, 25].

Post remission therapy

When a CR is achieved further treatment is needed to reduce or eliminate residual leukemic cells. Several recent trials have shown that in younger patients a cure rate of about 40% can be achieved when intensive consolidation chemotherapy is administered [6, 8, 26, 27]. Interestingly, quite different consolidation protocols seem to have the same efficacy (Figure 3). Consolidation protocols based only on high dose ARA-C [26] were equally effective as protocols which use alternating cycles with non-cross-reacting drugs [6, 8, 27]. It is also not clear how many cycles are required and whether some protocols are particularly effective in certain subtypes of AML.

An important type of consolidation treatment is allotransplantation and autologous bone marrow transplantation (BMT). Randomised trials which have evaluated the efficacy of autologous stem cell transplantation in first CR have yielded conflicting results. While the EORTC trial [28] and the MRC 10 trial [29] showed superior disease free survival compared to intensive chemotherapy, an improved disease free survival could not be demonstrated in two other trials [27, 30]. A significant improvement of the overall survival could not be demonstrated in any of the trials, which was partly due to the high treatment related mortality.

Allogeneic BMT with a sibling or a matched unrelated donor is a highly effective consolidation therapy but associ-
ated with considerable toxicity and reduced quality of life in some patients. Allogeneic BMT is clearly indicated and the treatment of choice in subgroups of patients in second CR or early relapse [24]. There is less agreement whether all patients with a sibling donor should undergo BMT in first CR [31]. We believe that patients with a favourable karyotype who have achieved a molecular remission (PML/RARα, CBFβ/MYH 11) [23, 32] should be treated with chemotherapy and receive BMT only in second CR. There may also be good reasons to defer sibling BMT in older patients (> age of 45 years) because of the risks of treatment related morbidity and mortality. BMT with an unrelated matched donor is currently not routinely done in first CR, but may be considered in patients with unfavourable karyotype with an expected poor outcome with chemotherapy.

Since more than 2/3 of younger patients have a sibling or unrelated matched donor allogeneic BMT plays an important role in the treatment strategy of AML. When the overall efficacy of therapy and the chance of cure in AML is evaluated, chemotherapy and BMT should be viewed together in survival analyses. Using all options of postremission therapy the chance of cure in patients below the age of 50 years may be more than 50% (Figure 4).

**Treatment of acute lymphoblastic leukemia (ALL)**

**Induction therapy**

The induction therapy consists of prednisone, vincristine and an anthracycline (in most studies DNR) [33]. The addition of asparaginase does not increase the CR rate [34], but is believed that it increases the quality of remission [35]. In most protocols prednisone is given daily for 20 weeks and DNR and vincristine in weekly intervals, but in recent protocols [36, 37] DNR was administered in an AML-like fashion (at days 1 to 3) with good results. The optimal dose and schedule of DNR is unknown. Intensification of the induction protocol
Figure 4. Total therapy in AML (chemotherapy, ATRA, allogeneic bone marrow transplantation) – Overall survival 1994–1998 (n=36, age < 50 years).

Figure 4 Total therapy in AML (chemotherapy, ATRA, allogeneic bone marrow transplantation) – Overall survival 1994–1998 (n=36, age < 50 years).

by addition of cyclophosphamide or high dose ARA-C [38] increased the toxicity without improvement of the CR rate.

In most recent trials a CR rate of > 75% has been achieved [35–43]. Older patients and those with the Philadelphia chromosome have a lower remission rate [35, 44]. Of the patients who do not achieve CR, about half have resistant disease and the other half die from complications. In order to reduce the rate of infections due to neutropenia we have carried out a randomised study in which the efficacy of G-CSF as adjunct to induction therapy was tested [42]. The G-CSF treated patients had a significantly shorter duration of neutropenia and more importantly a significantly reduced incidence of infection. The CR rate was not increased. The study also has shown that with G-CSF relatively high doses of DNR (50% more than in the GMALL protocol) can be tolerated without excessive toxicity. G-CSF did reduce also the incidence of infections in phase II of the GMALL protocol and allowed to administer chemotherapy without delay [45]. In the study of Larson et al. [37] G-CSF was given in an AML like induction protocol after daunorubicin and cyclophosphamide. Time of neutropenia was shortened and there was a marked reduction of toxic deaths in patients older than 60 years.

Postremission therapy

From non-randomised and a few small randomised studies there was some evidence that intensive early consolidation may be associated with better outcome. The efficacy of early consolidation has been definitely proven by the recent UKALL XA trial [36]. Patients in CR were randomised into four groups: no consolidation, early consolidation alone, late consolidation (after 20 weeks) and early plus late consolidation. Patients who had received early consolidation had a significantly better disease free survival than patients without consolidation or only late consolidation. Late intensification has also not improved the outcome in an other trial [46]. Less clear is which drugs should be given as consolidation therapy. From a retrospective comparison of various trials there is good evidence that cyclophosphamide and ARA-C play an important role in the management of T-cell and considerably improve the DFS [35]. High dose ARA-C and mitoxantrone may be effective in the t(4;11) patients.

After consolidation therapy maintenance therapy is usually given for 2 years, and consists of purinethol and methotrexate. In some protocols pulses of prednisone and vincristine were given. The need for maintenance therapy has never been tested in a randomised trial in adult ALL. In two recent protocols which consisted of intensive induction and consolidation therapy without maintenance therapy good long term results were achieved which were comparable to protocols with maintenance therapy [39, 41]. In the future it may be possible to tailor the duration of treatment according to the presence or absence of minimal residual disease [47].

CNS prophylaxis is an important part of ALL therapy. CNS leukemia at diagnosis is less frequent in adults (< 10%), but without prophylaxis a quarter to half of patients have CNS relapses. CNS prophylaxis consists most often of intrathecal application of methotrexate and/or cytarabine and cranial irradiation. Intravenous high dose cytarabine or methotrexate may also be effective. Despite appropriate prophylaxis the CNS relapse rate is around 10% [48].

In recent trials a disease free survival between 25% and 46% at 3 to 10 years has been reported [35–37, 39, 40, 41, 46, 49]. The treatment results in our centre are shown in Figures 5 and 6. The most important risk factors are age, immune phenotype, time to achieve a complete remission and karyotype [50]. Patients over the age of 50 have a very poor prognosis (poorer than in AML) which is explained (but only
partly) by the high prevalence of Philadelphia chromosome in this age group. Patients with T-ALL have a better prognosis than with B-lineage ALL. An early response to induction therapy is a good prognostic factor [51] while patients who achieve a CR beyond 4 weeks of therapy have a dismal prognosis [50]. Patients with a Ph+ or t(4;11) have a very poor prognosis. Adults with Ph+ ALL cannot be cured by chemotherapy, but may achieve long term remissions after allogeneic bone marrow transplantation [52]. Some patients with t(4;11) may be cured by chemotherapy when PCR negativity is achieved.

The role of BMT is less clear in ALL than in AML. In case control [53] and prospective studies [49] allo BMT did not result in improved disease free survival and overall survival. While there are fewer relapses after allo BMT this is outweighed by an increased treatment related mortality. However, Ph+ ALL is a clear indication for allo BMT in first CR with a sibling or MUD donor, because this is the only chance of cure [52]. It is unclear whether a BMT should be done in first remission in the presence of other risk factors. Auto BMT is not superior to chemotherapy in adults in first complete remission [38]. Studies are in progress in which Ph+ patients are autotransplanted with Ph- peripheral stem cells which were collected in the early phase of recovery after intensive chemotherapy [54]. Allogeneic BMT with an unrelated donor may cure a substantial proportion of patients in second remission [55]. Since no new potent antileukemic drugs are likely to be available in the near future, an improvement of treatment results can only be expected by a more extensive use of allogeneic BMT with matched unrelated donors combined with efforts to reduce the toxicity of this procedure. In acute myeloid leukemia autotransplantation with peripheral stem cells may reduce the complication rate without the result that the reduced relapse rate translates in improved overall survival. Another promising approach may be generation of cytotoxic T-cells which could remove or control residual leukemic cell after intensive chemotherapy.

References


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