Opinion Statement

Maintenance treatment for AML is an approach to minimize residual disease, optimize quality of remission and prevent a leukemic regrowth over a longer period of time. This intention implies a certain antileukemic activity and myelotoxicity. Thus, a prolonged myelosuppressive maintenance is best exemplified by the optimized protocol of the CALGB published by Kanti R. Rai in 1981 (Blood 58:1203–1212, 1981) and derived by the AMLCG as a therapeutic standard. From our today’s knowledge about the impact of various strategies, a lack of postremission therapy is not compatible with durable remissions. Even after an induction-type consolidation, the classic CALGB-type maintenance, or a comparably intensive regimen improved the relapse-free survival over that from alternatives. Some studies which failed to show a benefit used maintenance at low-dosage or short duration. Data about maintenance delivery in patients reaching long-term remissions demonstrate feasibility and compliance, and a low maintenance-related death rate can compete with that from alternative options. Revisiting maintenance, however, requires a comparison with other strategies on the basis of intention-to-treat. Either single prospective trials or crosstrial networking by a common standard arm and general upfront randomization can further assess the relative value of maintenance for AML.
Introduction

Revisiting maintenance therapy for AML is becoming necessary since established alternative options have not clearly improved the cure of this disease. Except for higher cure rates in acute promyelocytic leukemia treated with ATRA or ATO [1,2] and CBF leukemias under intensive chemotherapy [3•] both accounting for 10% and 10% of AML, respectively, the remaining 80% of patients with AML show an overall survival (OS) of 30–40% at 3 years with less than 50% even in younger and only half that in older patients, as from unselected study populations [4]. Patients over 60 years, however, contribute 2/3 of the entire AML population [5,6] and up to 50% to large multicenter trials [4]. Restricted to younger patients, an advantage of autologous transplantation has been found in highly selected groups [7]. While some encouraging results of allogeneic transplants [8–10] have the inherent problem of incomparability, intention-to-treat analyses of comparable groups such as patients with histocompatible sibling donors and those with siblings but no donors are still owing. Similarly, a randomized assignment to unrelated donor transplantation versus alternative treatment in patients with matched unrelated donors has not been done.

Thus, the relative value of maintenance treatment should be questioned, after many therapies and trial groups abandoned this option and/or decided for a form of chemotherapy other than maintenance. Maintenance denotes a prolonged cytotoxic treatment in complete remission and differs by a lower dosage from induction-type consolidation or high-dose consolidation. Administered either continuously or in periodical courses, maintenance is a strategy to further reduce the residual leukemia, improve the quality of remission, and prevent or delay the regrowth of leukemic cells associated with relapse. Since different trials follow this intention by various medication, dosage, and intervals, we here give an overview of major randomized trials on maintenance and their essential modalities.

Maintenance in randomized trials

- Monthly myelosuppressive maintenance as investigated in an early trial by the CALGB [11•] and further used in some recent trials [4,12] can serve as a model of maintenance more generally. Starting in 1974 Rai and colleagues treated 358 patients of all ages for induction by standard dose araC + DNR in 4 randomized variables of which the combination of araC 100 mg/m²/d by continuous i.v. infusion on days 1–7 plus DNR 45 mg/m²/d injection on days 1–3 was found the best induction regimen. For monthly maintenance, araC 100 mg/m² q 12 hours on days 1–5 was combined either with thioguanine 100 mg/m² q 12 hours p.o. on days 1–5 (1st month), or with cyclophosphamide 1000 mg/m² i.v. bolus on day 1 (2nd month), or with CCNU 75 mg/m² p.o. on day 1 (3rd month), or with DNR 45 mg/m²/d i.v. bolus on days 1 and 2 (4th month), repeated monthly at the same sequence for 4–5 years. After reaching a potential cardiotoxic cumulative dosage DNR was omitted. By randomization, araC in maintenance was given either i.v. or s.c. of which the s.c. variable proved superior. Repeated persistent neutropenia or thrombocytopenia justified a permanent 50% dose reduction for all drugs which was necessary in 1/2 to 2/3 of patients. The combination of araC infusion for induction and s.c. injection for maintenance was associated with significant superior survival (SV) and remission duration (RD).

- In their 1978 pilot study the AML Cooperative Group (AMLCG) nonrandomly compared different types of postremission therapy. While the 133 patients receiving any postremission therapy showed 24% ongoing CR at 4 years, all 37 patients without treatment in CR relapsed early (Fig. 1) although 2/3 of them remained untreated for reasons other than early relapse [13].