



## Therapy of acute myeloid leukemia: towards a patient-oriented, risk-adapted approach

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### ABSTRACT

**Background and Objective.** The successful use of differentiating treatment for patients with acute promyelocytic leukemia (APL) suggests that other acute myeloid leukemias (AML) may benefit from tailored and subtype-specific therapy. Despite the fact that new drugs specifically targeting AML genetic lesions have not yet been developed, distinct karyotypic categories have been identified which may deserve differentiated treatment. In addition, molecular assays to assess response to therapy more sensitively are now available for several AML subsets. In this review, we discuss the role of genetic characterization in the therapy of AML, and the investigative efforts which we believe are still needed for the design of tailored treatment for each and every patient with this disease.

**Design and Methods.** The authors have been working in this field for many years and have contributed original papers, the data of which are incorporated in this article. In addition, the material analyzed in this overview includes articles and reviews covered by the Science Citation Index® and Medline® as well as some more recent unpublished personal observations.

**Results.** Modern therapeutic approaches to AML tend to differentiate post-induction treatment intensity according to cytogenetically defined risk categories. Such prognostic categorization is largely unsatisfactory. In fact, following the advent of newly developed molecular assays (e.g. RT-PCR and FISH), specific and prognostically relevant lesions are frequently found in patients with an apparently normal karyotype, and these patients are, therefore, re-assigned to more appropriate prognostic categories. In addition, recent studies suggest that some patients may benefit from an increase in induction intensity; rapid genetic characterization will be needed for future differentiation of initial therapy. However, preliminary investigation of AML by integrated karyotypic/molecular analyses show that no specific abnormalities are detectable in at least half of the cases. Therefore, use of genetic criteria for prognostic stratification is currently feasible in only a proportion of patients.

**Interpretations and Conclusions.** The prognostic role of genetic lesions, currently identified by karyotypic studies, needs to be validated in large series of AML patients prospectively characterized by advanced

molecular/cytogenetic analyses and treated uniformly. In addition, searches for new clinically relevant genetic abnormalities, and diagnostic tools for their rapid identification are urgently needed to identify prognostic categories better. Elucidation of AML gene alterations should foster basic investigation aimed at developing new drugs targeted to the specific lesion in the individual patient. Before these more specific therapeutic agents are developed, diagnostic genetic characterization should add to other well-established prognostic factors to optimize the use of the presently available therapies.

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### Modern approaches and controversial issues in the therapy of acute myeloid leukemias

Until recent years, treatment of acute myeloid leukemia (AML) consisted of a standard two-drug induction phase followed by various post-remission options whose intensities were based mainly on the patient's age and eligibility for bone marrow transplantation (BMT). While allogeneic BMT has been regarded as the best option for patients with an HLA-identical donor, major controversies surrounded the choice between autologous transplant or chemotherapy to consolidate remission in those without. Before the 90's, no biological features of leukemic cells substantially influenced therapeutic decisions.<sup>1-4</sup>

During the last decade, cytogenetic features have been increasingly regarded as relevant indicators of response to therapy and clinical outcome in AML,<sup>5,6</sup> and several investigators nowadays consider karyotype at diagnosis as a major criterion for post-remission therapeutic stratification. Two large multicenter studies conducted in the USA (CALGB)<sup>7</sup> and in Europe (MRC)<sup>8</sup> in which cytogenetic characterization was available for the majority of enrolled patients, have clearly indicated a fairly variable clinical outcome depending on the diagnostic detection in AML blasts of poor, intermediate or favorable karyotype (see below for definitions). As a consequence, new therapeutic trials have been initiated

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(or are presently being planned) which investigate distinct post-remission options according to karyotypic group given after a standard induction phase. In particular, it is being suggested that patients with good-risk cytogenetic abnormalities could be spared highly toxic and more life-threatening approaches such as allogeneic BMT, since they might achieve long-term remission with chemotherapy alone.<sup>9-11</sup>

A further issue which has generated considerable interest in recent years is the type and intensity of induction.<sup>12</sup> Although idarubicin appeared better than daunorubicin in preliminary randomized studies,<sup>13-15</sup> the advantage of one intercalating agent (including mitoxantrone) over the other, is still uncertain and currently under investigation in larger randomized trials. The addition of a third drug such as etoposide to the standard cytarabine plus anthracycline protocols<sup>16</sup> and, more recently, the use of high-dose cytarabine in induction,<sup>17,18</sup> resulted in improved outcome. Interestingly, these regimens positively affected the disease-free survival without affecting the remission rate, suggesting that a better "quality" of remission is obtained with these strategies.<sup>12,16-18</sup> Other approaches for intensifying induction include the prolongation of standard cytarabine dose from 7 to 10 days (the superiority of this approach was not, however, proven in a randomized trial)<sup>19</sup> and the so-called "timed-sequential therapy", which exploits early administration of cell cycle-specific agents at the time of maximal recruitment.<sup>20-22</sup>

Despite the promising results reported in some studies,<sup>17,18</sup> it is not yet clear whether intensification of induction is more advantageous than a theoretically safer intensification of the post-remission phase. In addition, the best type and intensity of consolidation therapy for patients receiving high-dose induction treatment has yet to be determined.<sup>12</sup>

Finally, refractory disease and early relapse remain a major challenge in AML therapy.<sup>11</sup> Recent studies with fludarabine in combination with cytarabine and G-CSF have reported interesting results,<sup>23-24</sup> although their superiority over more traditional salvage regimens such as high-dose cytarabine and mitoxantrone<sup>25,26</sup> is questionable.

In this article, we will review the potential role of genetic studies in addressing AML therapy. Current knowledge on the prognostic significance of genetic abnormalities will be analyzed in conjunction with other well established prognostic factors in an attempt to design provisioned specific algorithms for particular subsets. Finally, we will try to identify what basic and clinical research efforts are still needed for the future design of tailored, risk-adapted treatment in different groups of patients.

### **The acute myeloid leukemias: diagnostic work-up**

Since the substantial biological and clinical differences have a major impact on treatment choice, three

main subsets of AML are currently distinguished, i.e. acute promyelocytic leukemia (APL) (at any age), AML in younger patients and AML in the elderly. Most trials have set an age cut-off at 60 years for differentiating treatments in non-M3 AML, although considering biological age is certainly more appropriate for patient enrolment in more or less aggressive protocols.

Compared to younger ones, elderly AML patients have a poorer prognosis due to a number of factors, including: i) poor performance status and tolerance to chemotherapy; ii) frequent evolution from antecedent myelodysplasia; iii) higher incidence of unfavorable karyotype; iv) more frequent multidrug resistance phenotype; v) poor marrow reserve.<sup>27-29</sup>

Diagnostic studies should enable rapid discrimination of APL cases which require prompt administration of a specific ATRA-containing treatment.<sup>30</sup> In our experience, reverse-transcriptase polymerase chain reaction (RT-PCR)-based detection of the specific PML/RAR $\alpha$  is the most convenient diagnostic approach, due to its additional capacity of precise definition of targets for minimal residual disease monitoring (PML breakpoint identification).<sup>31</sup> All cases which are morphologically and/or immunophenotypically (i.e. DR-ve/CD9<sup>+</sup>) suspected to be APL are subjected, in our Department, to molecular search for this specific lesion. Use of the anti-PML monoclonal antibody PG-M3 is equally advantageous and allows more rapid diagnosis,<sup>32</sup> whereas karyotyping requires long-lasting cultures to be set up. In addition, t(15;17) may escape karyotypic detection due to poor quality metaphases or cryptic rearrangements.<sup>33</sup>

While patient age reflects biological and clinical heterogeneity in AML and influences treatment decision, no substantial clinico-biological differences are observed in APL patients who should receive the same therapy regardless of age. Moreover, response to treatment and overall outcome are considerably better in elderly APL patients than in age-matched patients with other AMLs,<sup>34,35</sup> indicating that genetic features are more reliable prognostic indicators than age, particularly when drugs targeting the specific molecular lesion are available.

Apart from recognition of M3-AML, morphologic distinction of FAB groups and immunophenotyping have little clinical relevance for initial therapeutic stratification. However, both analyses are essential in the light of their potential to identify particular subsets (e.g. AML with trilineage myelodysplasia, minimally differentiated (M0) AML, megakaryoblastic (M7) AML) and/or aberrant co-expression of markers which may be used as targets for minimal residual disease monitoring.<sup>11,36</sup> Karyotypic characterization should be mandatory in all cases and results are currently used in several Institutions for differentiating post-remission therapy. The most relevant AML subsets to be identified at diagnosis for therapeutic stratification are shown in Table 1.

**Table 1. Diagnostic work-up in AML: identification of specific subsets.**

Methods	Subsets	Induction*	Post-induction <sup>o</sup>
Morphology Immunophenotype RT-PCR Karyotype	APL	tailored	tailored
History	secondary AML	standard or investigational	aggressive
Morphology	trilineage MDS AML	standard or investigational	aggressive
Karyotype/FISH	- 5; -7; 5q-; 7q-	standard or investigational	aggressive
Karyotype RT-PCR	t(8;21) or inv.(16)	standard	less aggressive (?)

\*<sup>o</sup>Detailed tailored induction and post-induction therapy for APL, and of standard/investigational, aggressive or less aggressive therapies for the other subsets are given in Figure 2.

### Genetic lesions of AML: clinical relevance of fusion genes

Most of our knowledge on the genetic features of AML is derived from conventional karyotyping.<sup>37-43</sup> In addition to providing a highly standardized and reproducible tool for the identification of distinct AML subsets, karyotypic characterization has represented, and still represents, an extremely useful starting point for the development of cloning strategies aimed at identifying new genes involved in the pathogenesis of AML. Moreover, even in the era of the widely employed RT-PCR or FISH assays for the detection of recurrent translocations, standard karyotyping on banded metaphases should not be regarded as obsolete, due to its potential to provide relevant additional information, both qualitative and quantitative, on leukemic cell aberrations. It is unfortunate that the advent of molecular diagnosis might somewhat negatively affect the interest of hematologists and laboratory researchers in conventional cytogenetics. Table 2 shows the genetic alterations most frequently detected in AML, the known genes involved at relevant chromosome sites, and the prognostic significance of each alteration.

The use of RT-PCR as a complementary diagnostic tool for these and other fusion genes offers several advantages, including: i) the possibility of detecting cases with apparently normal karyotypes (cryptic translocations); ii) the dissection of further heterogeneity by identification of distinct breakpoints, and iii) more sensitive assessment of response to treatment and monitoring of minimal residual disease. Prospective studies aimed at determining the incidence of some chromosomal aberrations in AML as assessed by RT-PCR are under way. Preliminary observations in 100 consecutive non-M3 AMLs molecularly studied in

**Table 2. Most frequent genetic lesions of AML.**

Karyotypic lesion	Involved genes	Prognostic significance
t(8;21)	AML1/ETO	favorable (?)
t(15;17)	PML/RAR $\alpha$	favorable
inv.(16)	CBF $\beta$ /MYH11	favorable (?)
11q23/ v	MLL/ v	unknown (unfavorable ?)
-5; 5q-	unknown	unfavorable
-7; 7q-	unknown	unfavorable
+8	unknown	unknown

v: variable partner.

**Table 3. Recently described fusion genes associated with AML.**

Karyotypic lesion	Incidence	Involved genes	Prognostic significance
t(11;17)	<1%	PLZF/RAR $\alpha$ NuMA/RAR $\alpha$	unfavorable ?
t(5;17)	?	NPM/RAR $\alpha$	?
t(3;5)	1%	NPM/MLF1	?
t(3;v)	?	EV11/ v	unfavorable
t(6;9)	1%	DEK/CAN	unfavorable
t(11;16)	?	MLL/CBP	unfavorable
t(16;21)	1%	FUS/ERG	unfavorable
t(7;11)	1%	NUP98/HOXA9	?

v: variable partner.

our Department indicate an incidence of 8%, 12% and 7% of t(8;21), inv.(16), and 11q23 rearrangements, respectively (unpublished observations). Other fusion genes less frequently detected in AML include DEK-CAN, FUS-ERG, NPM/MLF1, PLZF/RAR $\alpha$ , MLL/CBP, NPM/RAR $\alpha$ , NuMA/RAR $\alpha$  and EV11/AML1.<sup>37-39</sup> Given their low frequency and/or recent description, the clinical significance of the majority of these alterations is unknown (Table 3).

As to numerical abnormalities, some of these have been unvariably associated with poor prognosis (e.g. partial or total deletions affecting chromosomes 5 and 7), whereas the clinical significance of other lesions, such as trisomy 8, is poorly understood.<sup>5-7</sup> Differently from chromosome translocations, the critical genes involved in these abnormalities have not yet been identified. For this reason, numerical aberrations are not easily amenable to molecular detection with gene-specific probes, while they represent ideal targets for FISH analysis.<sup>44-46</sup>

Taken together, cytogenetic abnormalities currently detectable by molecular analysis account for only approximately one third of non-M3 AMLs. Combining conventional karyotyping and FISH, and therefore the ability to detect numerical aberrations, this fraction may reach 40% to 45% of cases. Thus, from a clinical viewpoint it is important to consider that no genetic information is at present available in at least half of AMLs. This highlights the need to foster basic investigation aimed at identifying new genetic lesions in order to define prognostic categories better and to allow sensitive monitoring of response to treatment in a greater proportion of patients. With respect to molecular lesions such as deletions or point mutations, fusion genes are particularly relevant in the clinical setting. In fact, several of these abnormalities have been shown to be causally related to leukemia pathogenesis in animal models, and consistent evidence indicates that they represent primary events in leukemogenesis.<sup>37-39</sup> This implies that the hybrid proteins formed as a consequence of chromosomal translocations play a crucial role in initiating the neoplastic process and are maintained along tumor progression, as opposed to lesions characterized by loss of material or mutations, which may frequently be acquired during disease evolution.<sup>38</sup> Thus, fusion genes are primary and pathogenetically relevant tumor markers, always detectable in the entire leukemic cell population both at diagnosis and at relapse. For these reasons, and because they are qualitative, not quantitative changes, fusion genes are ideal markers which allow better targeting of therapy based on more specific and sensitive evaluation of remission.

### **Clinical features and outcome of AMLs affecting the core binding factor (CBF)**

Of all non-M3 subsets, AMLs affecting the core binding factor (CBF) complex are at present, the best characterized group. CBF, also known as *Polyoma Enhancer Binding Protein 2* (PEBP2), is a heterodimeric transcription factor formed by two unrelated subunits termed  $\alpha$  and  $\beta$ .<sup>47</sup> The  $\alpha$  subunit is encoded by the AML1 gene, which is involved together with the ETO gene in the t(8;21) translocation most commonly found in FAB-M2 AML,<sup>40,48</sup> while the  $\beta$  subunit is encoded by a gene, CBF $\beta$ , rearranged and fused to the MYH11 gene in the inv(16) aberration characteristically associated with FAB M4eo. AML.<sup>39</sup> Thus, interestingly enough, the two most common chromosome abnormalities of AML (taken together, they account for some 20% of cases) affect the two subunits of the same target protein, suggesting that the wild type CBF must exert an important role in the control of hemopoietic cell growth and/or differentiation.<sup>49</sup> Further interest in this protein was raised by recent evidence that other myeloid leukemias and, particularly, a high proportion of childhood lymphoid leukemias, are characterized by derangement

of the AML1 gene.<sup>50</sup> Indeed, the CBF complex represents, to date, the most common target of structural alterations in human leukemia.

Biological features of t(8;21) AML include the presence of hypergranulated and strongly myeloperoxidase-positive blasts, CD13, CD33 and CD34 expression, and frequent marrow eosinophilia.<sup>51,52</sup> Interestingly, positive staining with CD19 and CD56 has been reported in a sizable fraction of cases and CD56 was associated with unfavorable clinical outcome.<sup>53</sup> Other features are the frequent loss of a sex chromosome and a tendency to form extramedullary tumors.<sup>52</sup> As to response to therapy, patients with t(8;21) AML are reported to have a high remission rate and prolonged disease-free survival, being particularly responsive to high-dose cytarabine.<sup>7,8</sup>

The inv.(16) abnormality is found by karyotyping in 8-10% of AMLs and in 70% of M4eo. cases.<sup>5-8,41</sup> Given the technical difficulties in identifying this rearrangement by conventional cytogenetics, some karyotypically negative cases have been diagnosed by RT-PCR evidence of the CBF $\beta$ -MYH11 fusion gene. In addition, cases showing this abnormality outside the M4eo. subset have been reported.<sup>41</sup> Immunophenotypic studies have shown the frequent association of the T-cell molecule CD2 with other more consistently detected myeloid surface markers.<sup>54</sup> As reported for t(8;21) AML, inv.(16) is frequently found in association with additional cytogenetic abnormalities which, however, seem not to have prognostic significance.<sup>55</sup> Clinical characteristics of inv.(16) AML include the tendency to form granulocytic sarcomas (frequently in the small bowel) and a favorable response to chemotherapy, similar to that reported for t(8;21) cases.<sup>5-8,56</sup>

Given their clinico-biological similarities, t(8;21) and inv(16) AMLs (now frequently referred to as CBF AMLs) are usually analyzed together with respect to treatment outcome and regarded as a group deserving tailored therapy. The most recent and comprehensive clinical study on CBF AMLs was conducted retrospectively by Burnett *et al.*<sup>8</sup> within the UK MRC trial AML10. These authors analyzed the outcome of more than 200 patients with t(8;21) or inv(16), compared to that of patients with normal karyotype. With respect to this latter group, patients with t(8;21) had significantly higher CR rates (88% vs 98%,  $p=0.0006$ ), whereas both t(8;21) and inv.(16) had significantly better 5-year survival (71% and 61%,  $p=0.009$  compared with normal karyotype) due to a reduced risk of relapse. In the same study, no survival benefit was conferred by either autologous or allogeneic BMT, with respect to no further post-consolidation treatment, in CBF AMLs. Finally, for patients who relapsed, second remission rates were significantly higher in CBF AML than in the normal karyotype group.<sup>8</sup> Together with previously reported analyses (CALGB),<sup>7</sup> these data strongly point to the need to identify these patients for tailored treatment.

Besides the results of these two co-operative trials,<sup>7,8</sup> some level of clinical heterogeneity has also been reported in t(8;21) AML which may influence therapeutic decisions. For example, in children the prognostic outcome appears less favorable than in adults.<sup>57</sup> Furthermore, patients with extramedullary disease have a poorer outcome and may deserve tailored treatment with more intensive regimens combined with local radiotherapy. Finally, as mentioned above, other biological features such as CD56 expression may help prognostic discrimination of this apparently homogeneous group.<sup>53</sup> In the light of these findings, and considering that both the CALGB<sup>7</sup> and MRC<sup>8</sup> studies previously discussed were done retrospectively, it appears that the elucidation of the prognostic significance of t(8;21) and inv.(16) leukemias and the best treatment approach to these forms need to be investigated in large prospective studies employing molecular diagnostic tools.

### Open questions about the genetic characterization of AML

While chromosome translocations may identify some important clinico-biological entities, our current knowledge on AML genetic features is still largely unsatisfactory. In fact: 1) karyotypic studies on large series have not always included patients receiving homogeneous treatment;<sup>5-8,55</sup> 2) cytogenetic data obtained in some prospective studies are only available for a minority of patients;<sup>48</sup> 3) many cases defined as bearing a *normal karyotype* need to be re-examined by molecular studies to unravel submicroscopic/cryptic translocations; 4) there is a long list of rare or unreported chromosomal abnormalities, mostly observed as small clusters, the clinicobiological significance of which is unknown;<sup>48</sup> 5) finally, the critical genes involved in clinically relevant numerical abnormalities, including -7, -5, +11, +3, +4, +13, and partial deletions such as 5q-, 7q- and 17p- have not yet been identified.

### Design of provisional algorithms

Given the above discussed situation, it appears that times are still premature for tailoring therapy according to genetic criteria in all AML patients. Rather, it is possible to combine some presently available information derived from cytogenetic and molecular studies (e.g. poor risk karyotype,<sup>7,58</sup> RT-PCR evidence of t8;21 or inv.16) with other more traditional and sound clinical parameters (e.g. age, presence/absence of trilineage myelodysplasia or of antecedent myelodysplasia, ability to substantially clear leukemic blasts after one cycle of chemotherapy). This may allow the design of provisional algorithms adapted to particular subsets (Figure 1). Although the above mentioned genetic features are usually considered for post-remission stratification, we believe that some features associated with an extremely dismal outcome could be also taken into account in induction therapy. We will refer here, in the following, to adult AML and APL.

### Non-M3 acute myeloid leukemia

A standard three-drug induction including an anthracycline, etoposide or thioguanine, and prolonged (10 days) cytarabine probably remain the best front-line choice for all non-APL cases, regardless of age and karyotypic features. Intensified induction with high-dose cytarabine according to the ALSG trial<sup>18</sup> could be an alternative option for some selected patients showing one or more of the following poor prognostic features: chromosome 5 and 7 monosomy/partial deletion, chromosome 3q21-q26 abnormalities,<sup>58</sup> trilineage myelodysplasia, history of antecedent myelodysplasia or secondary AML. A further alternative in these poor prognosis categories is the front-line use of regimens including new drugs, such as fludarabine, presently employed as salvage therapy in refractory or relapsed AML. This regimen seems effective in AML subsets showing poor prognostic features.<sup>23,24</sup> Such stratification implies that karyotype should be available shortly after diagnosis in all cases. This should be logistically feasible considering that, with rare exceptions, AML patients need not receive immediate treatment, and oral hydroxyurea is an effective and commonly employed means for temporarily controlling significant hyperleukocytosis. Searches for unrelated donors should begin as soon as possible in these poor prognosis subsets.

Distinct post-remission options should be chosen taking into account the above mentioned clinico-biological criteria plus availability of an HLA-identical donor and patient eligibility for BMT. Intensive post-remission±autologous BMT (autoBMT)<sup>59</sup> is recommended for patient with t(8;21) or inv.(16) AML, even in the presence of an HLA-identical donor, and allo-BMT should be left to consolidate 2<sup>nd</sup> remission in these cases. Similarly, cytarabine-based consolidation followed by AutoBMT in first CR is advisable for patients who lack poor prognostic features at presentation, even in the presence of an HLA-identical donor. Patients with adverse prognostic features are candidates for allogeneic BMT (alloBMT) from an HLA-identical sibling or matched unrelated donor (MUD).

Patients with refractory disease, including those not responding to front-line treatment or those having early relapses (within 6-12 months from achievement of 1<sup>st</sup> CR), are candidates for investigational treatments followed, if aged < 55 by AlloBMT or matched unrelated BMT. Phase I/II trials of so-called *miniallografts* (i.e. non-T depleted alloBMT using less myelotoxic conditioning regimens including immunosuppressive agents such as fludarabine) are extremely interesting options for patients with poor prognosis AML in either 1<sup>st</sup> or 2<sup>nd</sup> CR.<sup>60</sup> Although the results are preliminary, this strategy seems promising due to its potential applicability also to patients aged >55.

Late relapses should be consolidated with ABMT or, if an HLA-identical sibling is available, with allo-BMT after reinduction. Chemotherapy regimens to be employed for reinduction are the same as indicat-

RELAPSE

POST-REMISSION

INDUCTION

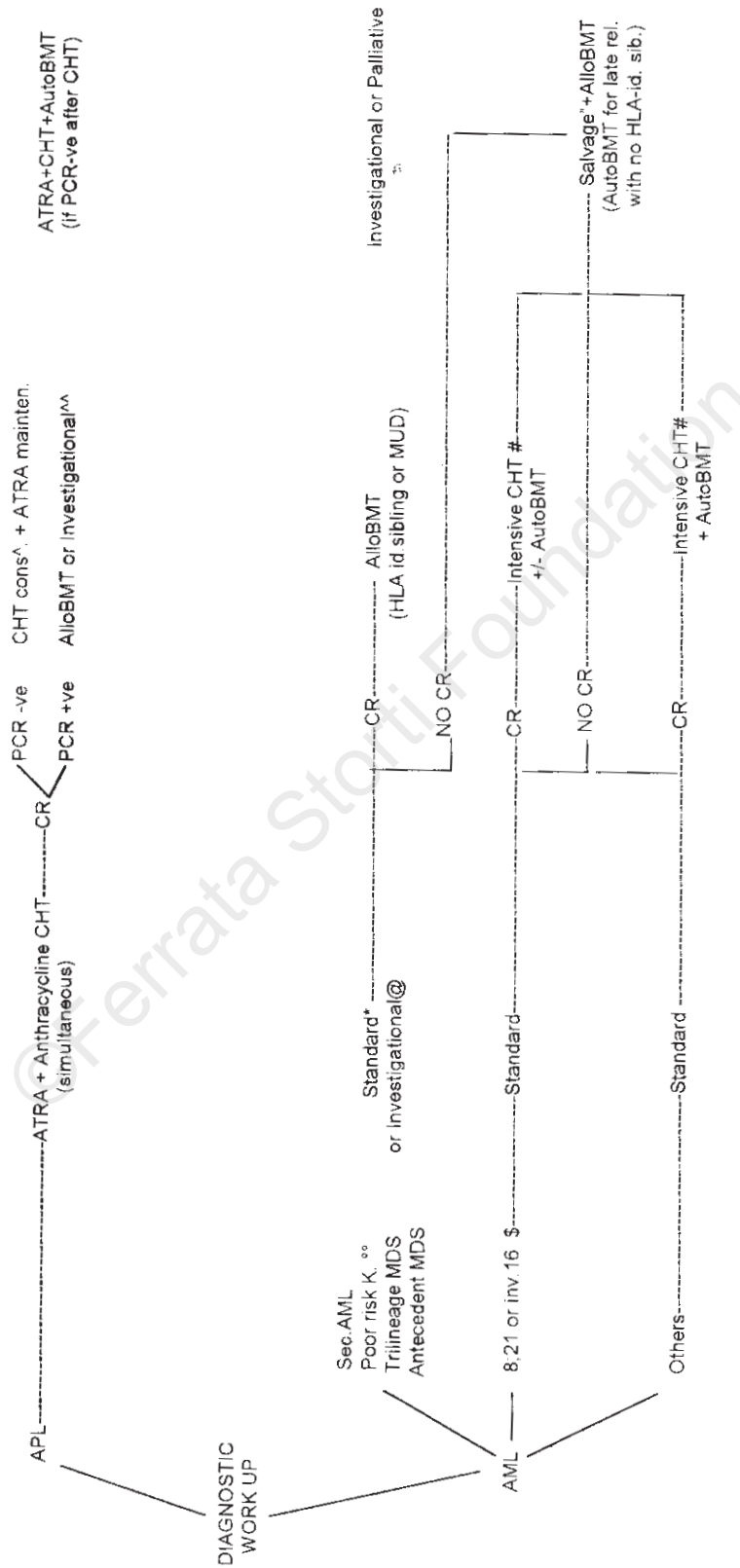


Figure 1. ^CHT cons. for APL should include high-dose of an anthracycline. ^^Investigational therapy for APL may include arsenic or novel retinoid derivatives. °°Poor risk K = defined in refs. #7 and 56. 8;21 and inv.16 \$ = defined by RT-PCR. \*Standard = 7+3 (cytarabine + an anthracycline) ± a third drug (e.g. 6-TG or VP16). #Intensive CHT for AML, should include high-dose cytarabine. °Investigational therapy for AML, may include novel agents (fludarabine, 2-CDA, topotecan etc.). "Salvage = HidAC, MEC or FLAG regimens.

ed above as salvage treatments for refractory AML.

### Acute promyelocytic leukemia

Tailored therapy including the simultaneous administration of ATRA and anthracycline-containing chemotherapy should be started promptly after demonstration of the APL-specific PML/RAR $\alpha$  hybrid gene and followed by intensive anthracycline-based consolidation. Patients achieving molecular remission at the end of consolidation should not undergo a transplantation procedure. According to the preliminary results of several multicenter trials, ATRA-containing maintenance seems to prolong relapse-free survival.<sup>61,62</sup> Accurate molecular monitoring during follow-up is extremely important, particularly in the early post-consolidation phase, as it allows early detection of minimal disease recurrence (conversion to PCR positivity) and this latter is invariably followed by hematologic relapse.<sup>63</sup> Anticipation of salvage therapy at the time of molecular relapse with ATRA followed by consolidation and autologous BMT might result in prolonged second remission according to preliminary results from the GIMEMA group.<sup>64</sup>

### Future perspectives

Genetic-tailored therapy of AML is at present possible, as we have seen, only in APL patients. The existence of a molecular aberration in all cases, and the availability of an agent (ATRA) specifically targeting the abnormal protein, represent a unique clinico-biological condition in human cancer. Such a condition not only allows a more rational treatment approach directed against the very protein responsible for the APL pathogenesis, but also enables us to adapt treatment intensity and timing of re-intervention by analyzing a specific tumor marker, rather than relying on the morphologic evaluation alone.

A special effort in both basic and pre-clinical research is needed before other AML subsets become amenable to similarly targeted therapies. This will initially require the identification and characterization of genes involved in that vast proportion of AML cases showing apparently normal karyotypes and/or less frequent aberrations of unknown significance. On the other hand, new agents directed against presently known and newly described abnormal AML proteins must be developed in the near future to pave the way to a more rational, hence less toxic, therapeutic approach. It is expected that the advent of such innovative strategies will also improve the outcome of elderly patients, whose extremely poor long-term prognosis still represents a major problem in the treatment of AML.

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FM was responsible for the establishment of treatment guidelines and supervised the manuscript. MCP provided substantial clinical information for patient management and contributed with critical reading of the manuscript. FLC was pri-

marily responsible for the conception of this review article and writing of the paper.

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