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What is the Best Chemotherapy Regimen for Mixed Lineage Leukemia or Biphenothpic Leukemia in Low or MiddleIncome?

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Introduction

Mixed Phenotype Acute Leukemia (MPAL) is a unequal subgroup in the World Health Organization classification that includes acute leukemia's with separate mixed populations of myeloid and lymphoid ("bilinear") or coexpression blasts large amounts of lymphoid and myeloid markers in a single population of blasts ("Biphenotypic"). The flow cytometrydatas suggestive of MPAL are often met with confusion by pathologists and oncologists, due to unfamiliarity with the disease and uncertainty about how MPAL fits into established paradigms for the treatment of acute leukemia[1].

The consensus criteria for the diagnosis of AMLL were established in 1995. The European Group for the Immunological Characterization of Leukemia (EGIL) has famous a scoring system for the immunological classification of acute leukemia. Base on the characteristics of the leukemic cells with respect to the expression of the antigen and the cellular source, the AMLL phenotype can be divided into bifenotypic, bilinear and biclonal types (including the type of conversion). In addition, other researchers have advised the morphological and cellular chemistry characteristics to support the calls AML Ly +or ALL My + [1]. But, in fact, the diagnosis of AMLL is very difficult and its clinical significance and prognosis are not entirely clear [2].(**Figure 1, Figure 2)**

There isn't a classical protocol for MPLA, so this article suggests best chemotherapy protocol for MPAL, as an unusual leukemia'sbased on actual documents.

Body of Article

Case reports from different centers or countries tend to test all cases of acute leukemia and describe MPAL in 2 to 3% of the population.

We treat with an ALL regimen and consolidate with an alloSCT if a donor isavailable.

Lineage	Markers
Myeloid	MPO (flow cytometry, immunohistochemistry, or enzyme cytochemistry) *-OR-* Monocytic differentiation (at least 2 of the following: NSE cytochemistry, CD11c, CD14, CD64, lysozyme)
T lineage	Strong[b] cytoplasmic CD3 *-OR-* Surface CD3
B lineage	Strong[b] CD19 with at least 1 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10 *-OR-* Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10

Figure 1: World Health Organization 2008/2016 Criteria for Mixed-phenotype Blasts [a]

Abbreviations: MPO, Myeloperoxidase, NSE, Nonspecific Esterase.

[a]Data derived from Borowitz et al.[6] and Arber et al. [7]

[b]Strong= at least as intense as in normal B or T cells.

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Points	B	T	Myeloid
2	cyCD79a cyCD22 cyIgM	CD3 (sm or cy) TCR-αβ TCR-γδ	MPO
1	CD19 CD20 CD10	CD2 CD5 CD8 CD10	CD117 CD13 CD33 CDw65
0.5	TdT CD24	TdT CD7 CD1a	CD14 CD15 CD64

Figure 2: European Group for Immunological Characterization of Acute Leukemias (EGIL) Algorithm for Biphenotypic Blasts [a,b]

Abbreviations: CY, Cytoplasmic; IGM, Immunoglobin M; MPO, Myeloperoxidase; SM, Surface Membrane; TCR, T-Cell Receptor; TDT, Terminal Deoxynucleotidyl Transferase.

[a]Biphenotypic leukaemia is diagnosed when scores are greater than 2 in 2 lineage columns.

[b]Data derived from Bene et. al. [5]

The Mostly complete remission rate is higher with ALL treatment or a combined ALL / AML chemotherapy regimen than with AML-type therapy even in many patients who had morphological AML (85% CR rate compared to 41% for AML type therapy). This phenomenon showed that the morphology of the explosion is not useful for the selection of the trend of the chemotherapy regimen (bases ALL or base AML). The etiology of this discorelated response is unknown [3,4].

While many of the suggestions have been to use ALL-type therapy, the situation is not always correct. Therefore, the use of the combined regimens of AML + ALL has some advises (the VAPA approach includes: vincristine 1.5 mg / m2, doxorubicin 30 mg / m2 for 3 days, prednisolone and Ara-C 100 mg / (m2 day) But some reports were found These regimens are quite toxic compared to the popular ALL. protocols [5].

Patients with MPAL when they achieve complete remission should have an allogenic SCT, depending on a high probability of early relapse. There was a 5-year OS rate of 70% compared to 19% for those who received chemotherapy alone.

Minimal Residual Disease (MRD) in MPAL cases can be challenging, although flow cytometry is administered to define MRD [6].

Patients who clearly have MRD at the beginning of their course may be managed by consolidation chemotherapy instead of allogenic SCT in a manner similar to ALL Ph+ that becomes molecularly negative after therapy. Chemotherapy alone would be insufficient to eradicate the disease[3-6].

MPAL is incurable without a stem cell transplant; the same probable Ph + AML and AML associated with MDS and / or adverse to the chromosome.

In MPAL, the initiation of treatment with ALL or a combined regimen is more logical than an AML regimen, especially the administer of Ara-C in the latter, less useful against a primitive stem cell that divides slowly [7].

Ph+and MLL Rearranged MPAL

The only special patients within the MPAL WHO classification are caseswith (9;22) or 11q23 cytogenetic abnormalities. Now, considerations chemotherapy for those with cytogenetic abnormality similar11q23 isnot different from those for MPAL with any non-Philadelphia cytogenetic [8].

However, the 11q23- rearranged cases should be advised to some novel agents if chemotherapy and allogenic HSCT fail or if the patient is not a candidate for aggressive chemotherapy. Such therapy could include a histone-modifying–enzyme inhibitor or an inhibitor based on the primary molecular abnormality or target therapy downstream activation of Hox genes via glycogen synthase kinase 3 or b-catenin inhibitors [3-10].

In Ph + MPAL we should use Tyrosine Kinase Inhibitor (TKI) such as Imatinib or Dsatinib combinated with chemotherapy followed by alloSCT.

This subtype is approximately 25% of all MPALs with poor prognosis. ALL Ph+ was historically considered an entity with poor prognosis, but prospective studies in which Imatinib or Dasatinib was combined with chemotherapy increased disease-free survival (DFS) from 40% to 60%. Although patients with Ph + ALL achieve remission with TKI plus chemotherapy and then they must be consolidated with alloSCT if there is a full compatible donor available [3-9].

Autologous bone marrow transplant for patients with ALL Ph+ in remission and / or TKI in progress since maintenance may be associated in the long termremission, if the patient has not full matched donor.

For older adults, excellent short-term results have been obtained with Dasatinib plus steroids and intrathecal chemotherapy[9].

Therefore, we treat all patients with MPAL with t (9; 22) by chemotherapy with age-specific ALL (CALGB hyperCVAD, MRC-ECOG) for middle-aged patientsand the FOA regimen for elderly patients in combination with a TKI followed by allogenic HSCT[10].

In some pediatric and adult reports, it was reported that biphenotypic expression was associated with a high frequency of involvement of the central nervous system (CNS) in the first presentation. The result of the use of pediatric-type chemotherapy plus TKI for cases under 40 years of age with MPAL + Ph is not clear[11].

The results of patients with MPAL PhAL with patients with Ph+ ALL showed a significant difference in completeremission rates between the 2 groups (100% vs. 85%), as well as a 5-year OS (55% vs. 53%) and disease free survival (DFS) (46% vs 42%)[12] (**Figure 3) (Table 1, Table 2).**

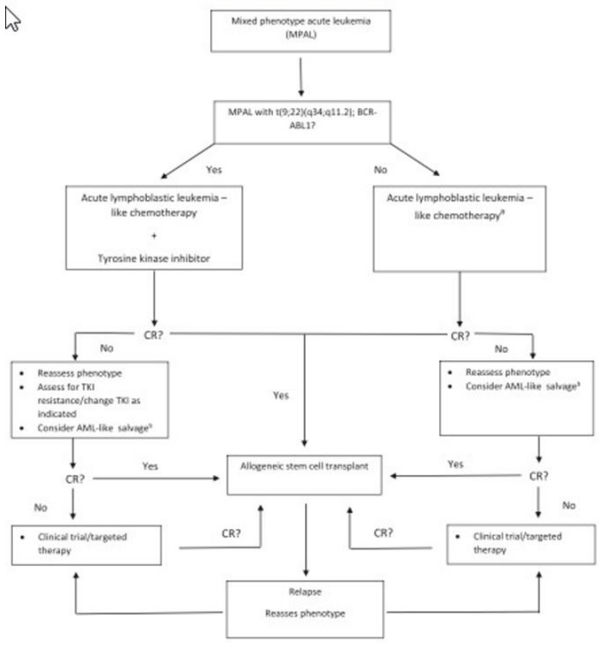

Figure 3: The approach to therapy in patients with mixed-phenotype acute leukaemia (MPAL). Targeted therapy based on a patient's specific genetic profile should be considered in refractaorylrelapse patients (eg. MLL rearrangements, FLT3-ITD, IDH1, IDH2).

[a]Consider Pediatric inspired protocol if <40 years old (in which case transplant in first remission not generally indicated)

[b] For example High-Dose Cytarabine and Mitoxantrone (HAM).

1. IT- Cytozar	day 0 ( )	
2. Daunorubicin	60 mg/m^2/day	(over 48 hrs continuous infusion) day 0( ), 1( )
3. Cyclophosphamide	1200 mg/m^2 IV	day 2( )
4. Mesna	1200 mg/m^2 IV	infusion/24 hrs days 2( ), 3( )
5. VCR	1.5 mg/m^2 IV (max. 2mg)	days 2( ), 9( ), 16( ), 23( )
6. prednisolon	60 mg/m^2/day po	days 2( ) to 23( ) then taper over 9 days
7. L-Asparginase	6000 u/m^2/day IM after skin test	days 4( ), 6( ), 8( ), 12( ), 14( ), 16( ), 20( ), 22( ), 24( )
8. IT -MTX		days 15( ), 22( )

Table 1: Induction (1 month)

Cytozar	1000 mg/m^2/doseIV Q12h	days 1( ) to 5()
Decadroneye drop	q4h	days 1-7
Etoposide	150 mg/m$^{2/dose}$IV infusion	days 1( ) to 5( )
IT Cytozar		day 1( )

Table 2: Consolidation (EACE)

Cytozar	3 gr/m^2 IV over 3 hrs	days 28( ), 29( )
Dexamethasone	Eye drop 4th times daily	days 28 to 31
L- Asparginase	6000 u/m^2/day 1M	days 28( ), 30 ( ), 32( ), 37( ), 39( ), 42( ), 44( ), 46( ), 48( ), 50( ), 52( ), 54( )
MTX	150 mg/m^2 IV over 4 hrs	day 31( )
VCR	1.5mg/m^2 IV (max 2mg)	day 32( ), 39( )
Prednisolon	180 mg/m^2/day (Max 100mg)	pofrom day32 ( ) up to day 39( )

Table 3: Line A (after BM recovery, if ANC > 500 and plt> 100,000)

Cytozar	1000 mg/m^2/doseIV Q12h	days 1( ) to 5()
Decadron	eye drop q4h	days 1-7
Etoposide	150 mg/m$^{2/dose}$IV infusion	days 1( ) to 5( )
IT Cytozar		day 1( )

Table 3: Line B if the patient is in remission after consolidation phase and the patient hasn'tfull Matched donor line C is recommend as targeted therapy.

If the patient is in remission after consolidation phase and the patient has full Matched donor line A is recommend,but if the patient is in remission after consolidation phase and the patient hasn'tfull matched donor line B is recommend **(Table 3 A, B).**

If the patient is in remission after consolidation phase and the patient hasn'tfull Matched donor line C is recommend as targeted therapy:

Conclusion

Mixed-phenotype acute leukemia is a diagnostic and therapeutic challenge owing to its heterogeneity, overlapping features with other types of ALL and AML, and lineage plasticity.Because MPLA patients are rare, controversial topicsabouttreatment of these patients are many .Weneed to many clinical trials to introduce safe and effective chemotherapy regimen which hasn't been mortality before bone marrow transplantation.

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