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Review Article

Maintenance Therapy in Oncohematology, 2020

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Abstract

Maintenance therapy has long been considered as the traditionally standard element of childhood and adult acute lymphoblastic leukemia protocols, but used less much less frequently and systematically in other malignant hematological disorders. As a consequence of the more recently available novel agents in first line, induction modalities and consolidation/maintenance turned and turns to be more and more a standard element of therapeutic protocols, tailored to molecular prognostic markers, along with minimal residual disease monitoring, leading to improved remission quality and duration. Consolidation-maintenance seems to transform into a more dynamic and complex approach. It is getting close to reaching a point of paradigm changes in quite a lot of conditions in which maintenance were not even routinely done, until quite recently. There are certain disorders in which maintenance used to be done and did not change meaningfully, like acute lymphoblastic leukemia. There are many conditions in which maintenance efforts are used as a standard of therapy, but recently new types of induction therapies, along with renewed maintenance attitude moved into guidelines, as in B-cell lymphomas and multiple myeloma. After many non-conclusive data, and because of no maintenance efforts, the scenario changed a lot in acute myeloid leukemia in special age groups, molecular cohorts with or without bone marrow transplantation modalities. In many conditions induction, consolidation and maintenance turned to be a non-independent complex, sometimes not sharply separated from each other or may even form a sort of continuum in some subgroups, like elderly multiple myeloma. Modern maintenance became more patient friendly, easy to use, quality of life based and need less and less hospital stay.

Keywords: Maintenance; Consolidation; Multiple myeloma; Kaplan lymphoma; Acute leukemia

Abbreviations

ALL: Acute Lymphoblastic Leukemia; CLL: Chronic Lymphocytic Leukemia; BTK: Bruton Kinase Inhibitor; DLBC: Diffuse Large B Cell Lymphoma; CAR-T: Cell Therapy, Modified T Cell Receptor Based Therapy; PET: Positron Emission Tomography; AML: Acute Myeloid Leukemia; ARA-C: Cytosine Arabinoside; MRD: Minimal Residual Disease

Introduction

Maintenance therapy used to be and still is the strong element of standard protocols for Acute Lymphoblastic Leukemia (ALL) after induction plus consolidation. In this case and other hematological disorders consolidation therapy traditionally defined as tool for deepening, improving the quality of the remission achieved by induction therapy. Conventional maintenance tries to attain the prolongation, longer duration of remissions, obtained by induction or consolidation, which in turn extends overall survival, postponing the relapse. Maintenance first was used mainly in diseases in which final cure was not possible, or impending early relapse might have been expected, and some sort of maintenance could have been achieved with more or less tolerable tools. In the era of the new agents and sensitive minimal residual disease methods, it became evident that remission quality can be improved by the so-called consolidation, and maintenance in much more malignant hematological disorders. Putting all this together, these efforts are gaining substantial survival benefit. There are some diseases with unchanged standard maintenance, in some disorders it is has changed a lot. In addition new maintenance therapy approach is more and more part of the treatment complexity of some acute myeloid leukemia more recently.

Maintenance change is not meaningful

Adult acute lymphoblastic leukemia: Daily 6-mercaptopurine and low dose methotrexate weekly or monthly basis consists the most standard element of childhood acute lymphoblastic leukemia. In adulthood, the induction therapies are highly variable, as opposed to the childhood period. This may affect consolidation therapy, which can be done in three major ways: Conservative chemotherapy, autologous transplantation, allogeneic transplantation [1]. Conservative consolidation therapy may be regarded as an acceptable option for adolescent and young adult patients and may be considered in all other patients with standard prognosis. There are no prospective, multicenter, comparative trials to establish the difference between the survival, following conservative consolidation therapy or transplantation. Historical data are showing quite similar results in survival rates [1]. Anyhow, there are many data outside of prospective trials, which are showing evidence that poor prognosis acute lymphoblastic leukemia patients even under the age of 35 years benefit from allogeneic transplantation, obviously also depending on donor availability. Post transplantation maintenance therapy is not recommended by international guidelines [1]. The only exception to this rule is the tyrosinkinase inhibitor administration post-transplant

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in Philadelphia positive acute lymphoblastic leukemia, with careful molecular follow-ups. Consolidation with autologous transplantation seems less convincing as a general recommendation, but can be applied in Philadelphia positive acute lymphoblastic leukemia, if stem cells harvested in 4.5 log bcr/abl reduction, and there is no suitable donor, or poor recipient biological condition [1].

Non-transplanted acute lymphoblastic leukemia after consolidation should receive 6-mercaptopurine daily, weekly methotrexate and monthly basis vincristine and prednisone. This is still the standard regimen for two or three years. According to clinical trials there is no benefit to extend this maintenance from 3 years to 5 [1].

Disorders and maintenance treatments, which used traditionally, but more recently substantially changed

Multiple myeloma: Historically with the use of melphalan/prednisone induction protocols remissions could not be achieved, just some more steady low-grade disease activity, the so-called plateau phase. That time the lengthening of plateau phase was the target in focus [2]. To achieve this goal and expand this plateau phase the main tools were interferons. These efforts proved to be quite efficient in some cases, but only in one-third of the patients. It proved to be unpredictable, that who will benefit from this regimen and who will not. It was supposed, that the patients with typical side effects (mild fever and muscle pain, flu like symptoms) would respond better (supposing immune mechanism against residual disease), but later on it became clear that this is not the case. Surface antigen structures were are also examined to anticipate the response. However, again it was not helpful [2]. Thalidomide was applied in French trials as maintenance, which anyhow was a big step forward. No doubt, this agent proved to be more effective, but in some cohorts of the patients, especially this translocation for 4/14 the relapses were more refractory, compared to the patient without maintenance, and this cohort of patients did not benefit from this form of maintenance in respect of overall survival at the end of the day [2,3]. It became an important issue, to analyze relapse treatment chances following maintenance, and select patients judging this, as well. Proteasome inhibitors, bortezomib first as such, was tried poor prognosis multiple myeloma. It was given less frequently and later on subcutaneously, to achieve better toleration on the long run. This kind of approach remained in use and probably it will play an important role in poor prognosis multiple myeloma for the time being and in the near future [3,4]. Of course new generation proteasome inhibitors especially ixazomibe, which can be given orally are very attractive, probably much more convenient and patient friendly. It is suggested to keep on proteasome inhibitor based maintenance until myeloma relapse [2]. In standard prognosis, multiple myeloma lenalidomide became the standard agent and tool, the standard dose is 10 mg for 21 days cycles. It is usually well tolerated; renal dysfunction might need dose reduction. French trials gave it usually in limited fashion to 2 years, but modern international guidelines recommend continue it until relapse, in all patient with standard risk multiple myeloma after transplant or without transplant consolidation [3]. The treatment of patients who are in relapse during lenalidomide maintenance is not an unresolved issue anymore, novel therapies and combinations proved effective in this condition [5]. Consideration should be paid to the association of slightly more secondary malignant conditions with myeloma patients on lenalidomide maintenance. The general risk is 1.6-time increase, mainly skin, lung myelodysplasia. This depends a lot on the age; elderly patients have a higher risk. A general survey of secondary cancer in myeloma found 16 cases per 10000 patient years in myeloma on lenalidomide maintenance course [6]. More importantly secondary malignancy depends a lot on the induction therapy, especially in elderly patients. Melphalan based induction increase the frequency of secondary tumors and myelodysplasia during lenalidomide maintenance. For this reason new non-transplant eligible induction therapeutic modalities are trying to avoid more and more melphalan based protocols. It is interesting to see that new recommendations in multiple myeloma patients, with age over 80 years and/or fragile condition recommend low dose dexamethasone plus lenalidomide induction. The dexamethasone dose should be low from the beginning: After a couple of cycles, only lenalidomide is administered further on until relapse. So in this case one may see that induction, consolidation and maintenance seems to be a complex approach, without sharp borders between therapeutic phases, rather like a continuum [7].

Indolent B-cell lymphoma, mantle cell lymphoma, Chronic Lymphocytic Leukemia (CLL): Mostly anti CD20 monoclonal antibodies have been tried as maintenance protocols in most of the cases during the last 15 years [8,9]. This is proved effective, resulted in prolonged survival, and still in use as a standard approach [10,11]. There are certainly some shortcomings, special limitations with vaccinations (some resistant Gram-positive strains, flu vaccine), few, but severe neutropenia episodes and low immunoglobulin levels along with inveterate upper airway infections. For the time being the new generation low-molecular-weight agents, which are used in induction of refractory cases or at relapse settings seem also promising as maintenance agents, but there is no evidence still coming from multicenter, prospective clinical trials to reinforce this view. Anyhow, in a primary refractory case it seems reasonable, to enter patients into clinical trials, or position them upon individual decisions to administer Bruton Kinase Inhibitor (BTK) inhibitor type, mainly ibrutinib (which might a good selection in COVID 19 era) as a part of both induction and probably maintenance. Presumably near future will provide much awaited data on other BTK inhibitors, e.g. acalabrutinib, zanubritinib (especially in patients with ibrutinib side effect problems or molecular resistance) or bcl-2 inhibitor (venetoclax, duvelisib) as induction/ maintenance. In indolent B cell lymphomas maintenance trends are visioning small molecules (BTK, bcl-2, etc. agents): in diffuse large B cell lymphomas the good responders are usually not receiving any kind of maintenance, as final cure may be achieved without that (few exceptions like leg-type lymphoma). The therapy primary refractory or relapsed Diffuse Large B Cell Lymphoma (DLBC) patients without molecular remission is still unresolved, the including of ibrutinib in younger patients into salvage protocols or modified T cell receptor based therapy (CAR-T cell therapy) are promising, but the follow-up or maintenance of good responders is still not defined clearly [12].

Hodgkin lymphoma: Hodgkin lymphoma was not a real target for maintenance, as excellent results are usually available with induction therapies resulting in final cure. However, still there are primary refractory or relapsed cases in which salvage therapy and autologous stem cell transplantation might help. In some cases is

difficult achieve complete metabolic remission (negative Positron Emission Tomography (PET) scan) prior to transplant without innovative agents, mainly brentuximab vedotin. In some cases post transplant brentuximab vedotin was applied [13]. This achieved benefit in reaching, completing or deepening remissions; however, overall survival benefit issue needs further follow-ups, especially in the light of sometimes quite significant neurological untoward effects. Overall survival results evaluation was hampered due to the cross-over fashion of AETHERA trial, in which non-responders could also receive brentuximab vedotin later on. However, this approach with brentuximab vedotin is a rather a consolidation, than a real maintenance [14].

Chronic lymphocytic leukemia: Lenalidomide and anti-CD20 molecules used to be tried most frequently. Lenalidomide maintenance in CLL came with significant adverse events, without solid proof of survival benefit. Rituximab (rituxane) maintenance was capable to obtain longer remission periods; however, overall survival benefit remained strongly questionable [15]. In the meanwhile a paradigm change took and takes place in CLL first line treatment approaches, including practically all molecular and genetic variants, i.e. start with BTK inhibitors (except patients aged 80 years, fragile patients), sometimes continued bcl-2 agents or others. These new ways of initial treatment probably will change and reform consolidation and maintenance in CLL substantially.

Diseases in which maintenance therapy became or turns to be standard element of therapy

Polycythemia Vera: Traditionally polycythemia vera therapy was based on regular phlebotomies and classical cytoreductive agents administration, in an effort to normalize blood counts/treat aquagenic pruritus, avoid vascular complications, and possibly to reduce fibrotic or Acute Myeloid Leukemia (AML) transformations. The first three goals are reached in most instances quite smoothly, however, transformation patterns did not change much, and some sort of cytoreductive agents may even possibly increase transformations risk. Innovative approaches are moving forward in polycythemia therapy; interferons are especially preferred in fertile or younger patients, or in cases with poor prognosis (some cytogenetic abnormalities, high Jak2 V617F mutated allele burden, etc.). More recently, PEGylated rope interferon alpha 2B observations described reduced secondary hematological malignancies, along with good quality molecular remissions (Jak2 burden went under 0.3%, i.e. detection level). Cessation of this agent was followed by relapses (at least in PROUD trial experience), but very low dose ropeginterferon alpha 2B, rather on monthly basis was able to maintain clinical and molecular regression, which attitude is resembling to a maintenance therapy [16].

Acute myeloid leukemia: The maintenance approach in AML used to be tried rather desperately since many years, mostly in vain [4,17-19]. The example was ALL, so 6-mercaptopurine and weekly methotrexate had been applied for this purpose in AML, too, but overall survival did not change at all [17,18].

Another traditional approach was immunological intervention to create maintenance (with the agents available by that time). Interferons and interleukin-2 (also approved by EMEA!) also failed to achieve consistent benefit in AML maintenance [20]. These approaches proved to be harmful after allogeneic transplantation routinely, as they may provoke GVHD, thrombotic microangiopathy [17]. Lenalidomide maintenance in transplanted AML carries similar risks [4].

It seemed also reasonable to try low dose cytosine Arabinoside (ARA-C) (147 patients received 10 mg pro sqm ARA-C twice daily for 12 days, 8 cycles) but prolonged survival could not be documented.

Further, on other ARA-C based traditional combinations, like vincristine, daunorubicine, etoposide, thioguanin, amsacridine or cyclophosphamide did not achieve convincing benefit [21].

As we gained more and more information about the genetic, molecular properties and background of AML new agents appeared as part or component of the traditional AML induction therapies, including young and elderly patients, as well, and some of these medications are tried or applied as a sort of AML maintenance more recently. AML maintenance might be used in Minimal Residual Disease (MRD) negative cases, following drug or transplant achieved remissions, but there are attempts to be applied in simple clinical/hematological complete remissions and may deepen and or probably prolong remissions [19].

Hypo ethylating agents: One of the most impressing, pioneering approach is oral azacitidine, UK trial selected more than 4000 mixed subtype, rather elderly AML patients, and applied azacitidine maintenance. Azacitidine maintenance was given in 75 mg/sqm oral doses for 5 days, 6 week courses. Five years overall survival did not improve in the entire patent population, but if patients were MRD negative average 5 years survival was 40.5% *versus* 13.5% in the placebo group [22]. Another type of approach to azacitidine maintenance made by the HOVON group: 50 mg/sqm subcutaneously, 5 days, six cycles were applied in elderly patients over 60 years with AML or myelodysplasia in complete or incomplete remission, (with and without transplant), which resulted in improved disease free survival (64% versus 42%), but not in overall survival [23]. Roboz and co-workers run a still ongoing trial (QUAZAR) on oral azacitidine in AML after remission, in patients over 55 years, preliminary results are promising [24]. At ASH 2019 QUAZAR data were presented as a late-breaking abstract, gained from 472 elderly (average 68 years, non transplant candidates) with intermediate or poor cytogenetic prognostic markers, with complete or incomplete remissions after induction. At 41 month timepoint median overall survival was 24.7 month (versus 14.8), while relapse free survival doubled. Azacitidine was applied mostly as 300 mg/day on days 1-14 and repeated after 28 days, and continued until the presence of >15% blasts, intolerance or need for transplant. These results were interpreted as a new standard of AML maintenance therapy.

Oral azacitidine had also been tried after allogeneic transplantation in AML patients [25], with pretty different maintenance schedules, in a small, rather heterogeneous patient population. It was well tolerated in respect of complications, graft versus host disease, and there were some positive results awaiting for confirmation in larger prospective multicenter trials. It is remarkable, that azacitidine may also help HLA-DR1 expression and trigger graft versus leukemia effects. The azacitidine trial run by Maples at in AML post-transplant was stopped, due to side effects and complications [26].

In summary: azacitidine might be a useful tool in AML maintenance, especially the oral formulation, which has better pharmacokinetics for (elderly?) AML patients, especially with MRD negativity. However, QUAZAR preliminary data are showing good results with different prognostic groups and different depth of first remission, but obviously more confirmatory data are needed, regarding the age group, dose schedule, quality of remission, and untoward effects in clinical settings outside of clinical trials. Poor prognosis myelodysplasia issue certainly also deserves more attention [27]. Post transplant azacitidine maintenance indication is still conflicting. Gemcitabine and venetoclax (the latter may be combined with azacitidine) are also remarkable approaches, trials are ongoing, especially following transplant [17].

Decitabine 20 mg/sqm for 5 days, for six cycles in core binding factor positive or negative AML patients achieved disease free survival 79% *versus* 54% in younger adults. In elderly patients the benefit was less evident with decitabine.

In TP53 mutated AML cases post-transplant APR-246 (able to induce apoptosis in TP53 positive cells), combined with azacitidine seems promising [17,19,28].

FLT3 positive cases benefit from sorafenib, midostaurin and quizartinib, and probably also with giltertinib [29,30,31]. This seems to be considered or recommended following transplant settings.

In IDH mutated cases evo/ivasidenib are important elements of induction efforts, and certainly will be useful tools in maintenance [28,32].

New type of immunological intervention is PD1, PD1 ligand modifiers, survival benefit with Nivolumab seems to be 18 month, but more data are needed in this field, and to consider the side effect profile, too [33].

Arsenic trioxide and retinoic acid might also be considered as a sort of maintenance in promyelocytic AML [17].

Classical maintenance rarely used

Chronic myeloid leukemia: Tyrosinkinase inhibitor treatment proved to be powerful enough in the vast majority of patients. Trends are moving into the direction to stop treatment in patients with high grade stable molecular remissions, and leave them without any kind of active or maintenance treatment. If allogeneic transplantation is needed in refractory or progressive disease, post transplant tyrosinkinase is frequently used as a sort of maintenance to prevent clinical/molecular relapse, but the initiation and duration is quite individual, depending a lot on blood counts and patient to patient variability of the disease.

Short conclusory remarks: This review tries to overview oncohematology maintenance categories, diseases in which, maintenance is not used, traditional maintenance remained unchanged or just renewed, or some indications like AML in which a new maintenance era seems to evolve, creating new way of thinking, new considerations and change of paradigms. Modern approach considers induction, consolidation and maintenance more closely depending from each other, and of course based more and more on molecular background and MRD data. The new agents, especially oral formulations renders maintenance more patient friendly, quality of life based and of course gain more efficiency. Hopefully generic compounds might make long term maintenance approaches even more feasible.

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