

Human immunodeficiency and Hodgkin lymphoma

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Abstract

Presentation of Hodgkin lymphoma (HL) is distinctive in the infected individual being more advanced, accompanied by B symptoms and the presence of extranodal disease particularly lymphadenopathy of the head and neck. Bone marrow involvement may be found in over 50% of cases. Virtually all co express gamma-herpesvirus. Phenotypically there is prominence of the mixed-cellularity and lymphocyte depleted histopathologic subtypes that define an aggressive clinical course in comparison to other variants. Prior to the induction of cART, median survival was only 1–2 years. Notably the first chemotherapy trial using ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in 21 patients, without treating the viral infection, resulted in a 43% complete remission rate accompanied by severe haematological toxicities but did not extend *median* survival with this being 1.5 years matching the negative cases.

Significant change accompanied concomitant anti-retroviral therapy that could be given safely even with dose intensive regimens exemplified by BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) in 12 patients or the Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone) coupled with involved-field radiation for bulky disease studied in 59 patients. BEACOPP extended overall survival (OS) to 83% at 2 years. A similar trend was seen

when using the Stanford V regimen with an OS rate of 51% at 3 years, disease-free survival (DFS) of 68% and freedom from progression (FFP) in 60%. Additional benefits accrued from supportive care with stimulatory peptides such as G-CSF and when combined with bacterial prophylaxis results approached that found in the uninfected reference group. Current consensus holds this particular lymphoma as still among the non-AIDS defining cancers being lung, stomach, liver or anal despite these having recently gained more attention as several of these neoplasms may be occurring more commonly in the era of cART.

While the relative risk of developing a non-AIDS-defining neoplasm in HIV-infected persons on the average is 2–3 times, the risk for developing HL in HIV-infected cases impressively ranges between 5 and 25 times when compared to the general population. Based on the precedent in which Kaposi sarcoma and the non-Hodgkin lymphomas distinctively alter the course of this retroviral infection in a way indistinguishable from concurrent Hodgkin lymphoma we propose that this entity be similarly regarded and the hypothesis tested in large randomised prospective study.

1. Introduction

Acquired immunodeficiency syndrome (AIDS) in the wake of infection with human immunodeficiency virus (HIV) was firstly described in homosexual men living in Los Angeles [1]. This was followed by reports of a markedly higher risk of developing malignancies such as Kaposi's sarcoma (KS) [2] and [3], primary cerebral and systemically occurring non-Hodgkin lymphoma (NHL) [4], [5], [6], [7] and [8] as well as invasive cervical cancer in those harbouring this virus, although the incidence of the latter malignancy has not increased as dramatically [9] and [10].

With the introduction of combination anti-retroviral therapy (cART) in 1996 [11] a modification not only on the morbidity and mortality related to HIV disease but also the spectrum of the different malignancies reported in HIV-infected patients has occurred. An increasing number of other neoplastic disorders including HL, testicular seminoma and lung cancer are still described as non-AIDS defining [12], [13] and [14]. Of note is a long-running Swiss study showing no increase in this particular lymphoma in recent years and also not among persons infected with the human immunodeficiency virus [15]. The same workers find no evidence of any increasing risk with improving immunity.

In this context is the role played by concurrent gamma-herpesvirus coinfection [16]. This distinction may be artificial given that most infected individuals live in sub Saharan Africa (SSA) where no plateau has yet been reached for infection rates [17] with South Africa in the midst of a pandemic having 5.5 million people testing positive [18]. Here malignant disease contributes significantly to morbidity and mortality particularly in this community [19]. The opportunity has therefore been taken extending our previous observations on KS and NHL [20] and [21] to examine a similar possible association for HL.

2. Epidemiology

Almost 20 years ago, Hessol and colleagues were the first researchers observing an excess number of Hodgkin cases among HIV-infected gay men associated with significantly worse outcome particularly higher mortality rates [22]. Cure rates for this lymphoma in the general population is expected to be in the range of 70–80% [23]. Thus a US based study carried out between 1988 and 1998 demonstrated a 5-year survival of 38% compared with 78% in negative matched cohorts [24]. Data from the United States or Europe contrasts with only few studies exploring the situation in the most affected regions.

For example, in a South African survey from 2005, overall HIV prevalence among the adults was 20% for females and 12% for males [25]: the risk of developing KS, NHL and HL was, respectively, 50, 6 and 2-fold higher when compared to the negative population. Despite this being the second most common cancer in Africa incidence remains small when in contrast to the 5–25-fold risk observed in western populations [26], [27] and [28]. Even so, none of the other tumour types examined being oral, liver or stomach cancer, melanoma, leukaemias or sarcomas showed a similar increased risk [25]. Furthermore, only few studies have provided information on HIV-infected individuals before progressing to AIDS [26] and [29].

This is important to note as the widespread use of cART since 1996 has not only led to dramatic improvements in immune status and prolonged survival among HIV-infected persons [30] but many may now never develop the overt syndrome. Nevertheless persons only marginally immunosuppressed may still be at excess risk of developing associated malignancies especially with extended survival. A recent study highlights the complex correlation altered immunity and cART in the face of HL [14]. The incidence of this lymphoma increased substantially following an AIDS diagnosis but also, somehow paradoxically, rose over time in association with the introduction of cART. Furthermore, the authors of the study conclude that, among people with this syndrome, the relationship between risk for neoplastic transformation and CD4 count is nonlinear [14].

Confirmation is therefore provided for results from prior studies describing an increasing risk over time subsequent to an AIDS diagnosis [27] and further elevation associated with the introduction of specific drug therapy [26].

3. Immunobiology, histological subtype and viral coinfection

The recognition of certain HIV related malignancies correlate with loss of immune control for latent infections with oncogenic viruses such as the human herpesvirus 8 (HHV 8) for KS or Epstein Barr virus (EBV) for selected NHL subtypes [31]. In HIV-infected HL patients EBV positivity can be found in almost all cases [24], [32] and [33], in contrast to the negative cohorts, in which this association has been observed in only 20–50% depending on histological subtype and age at diagnosis [34]. These findings were confirmed on molecular level by showing the presence of EBV-associated antigens as well as EBV-encoded RNA (EBER) and latent membrane protein-1 (LMP-1) [16] and [24].

Interestingly in the latter cases all histologic subtypes, other than nodular sclerosing, followed a more aggressive course [35] supporting the concept that the presence of both viruses adversely

affected survival [24]. The mechanism is postulated to reflect the induction of oncogenesis via production of the oncoprotein called LMP-1 released during infection of the lymphocytes [24] and [32]. This might explain the more virulent clinical characteristics and the predominance of the less favourable histologic subtype being mixed cellularity and lymphocyte depleted variants.

Immune reconstitution with cART is causing an increased risk for these tumours by shifting HIV-infected individuals to a level of immunosuppression associated with highest risk [27] and [28]. The Reed Sternberg (RS) cell seems to play a central role in facilitating such complex interactions. It was hypothesized that in severely immunosuppressed HIV-infected individuals usually presenting with CD4 counts below 50/ μ l these malignant giant cells cannot recruit lymphocytes and histiocytes, both usually known to produce proinflammatory cytokines, essential survival of this unique tumour cell.

With the increase in CD4 counts during effective anti-retroviral therapy (immune reconstitution) it seems that an overshooting, perturbed and nonlinear way of immunosuppression is needed for the manifestation of disease [28]. Oncogenesis of other HIV related cancers such as cervical, anal or hepatic is associated with specific co-viral infections caused by the human papillomavirus (HPV), hepatitis B or C virus but since even though these neoplasms arise at increased frequency the importance of immunosuppression is less clear [36] and [37].

4. Clinical findings and presentation

Hodgkin manifests more aggressively in the HIV-infected population. Bone marrow involvement has been documented in 40–60% at diagnosis, and may be the initial feature in about 20% of patients; therefore trephine biopsy should be obligatory [38]. An explanation could be that, in the setting of HIV infection, patients undergo this examination more often for the evaluation of obscure fever, night sweats, fatigue, weight loss as well as pancytopenia [39]. Atypical clinical presentations and unusual pathologic characteristics occur in 30–60% of HIV-negative individuals even with advanced stages of disease at diagnosis whereas then systemic symptoms are found in more than 70% once positive [39] and [40].

Furthermore, Poluri et al. [41] noted 100% of the HIV cases the involvement of head and neck regions in patients compared to 81% of non-HIV cohorts. Similarly 80% of cases had stage III and IV HD compared to 45% of the reference population. Also 75% had mixed cellularity subtype in contrast to 50% uninfected individuals. The swollen lymph nodes can get very large and the fever shows a characteristic rise and fall described as Pel-Ebstein, very often accompanied by anaemia and fatigue.

5. Diagnosis and staging

Lymph node or tissue biopsy of suspected lesions to confirm presence of the characteristic Reed-Sternberg cells is routine but should be always accompanied by bone marrow biopsy due to the high likelihood of involvement in patients. In order to minimize late effects without compromising efficacy, risk-adapted strategies, based not only on pre-treatment prognostic factors but also on the results of early restaging positron emission tomography (PET) scans have been recently developed [42].

Despite the superiority of the functional imaging, computed tomographic (CT) scans are still routinely used in the initial staging of HL. The reason for this anomaly could be that, although the former is preferred with an advantage in detecting lymphomatous lesions in a further approximately 15%, this “upstaging” effect will not result in a change of treatment strategies based on standard chemotherapy protocols as first-line treatment.

However, the role of more sensitive techniques has become more important in the restaging process after initiation of treatment where it was shown to influence prognosis and treatment outcome [43], [44], [45] and [46]. Although it is widely accepted that a positive interim PET reflects poor prognosis, it is yet unknown whether a change of therapy in these patients will result in improved survival. Also the false positive results await better understanding.

6. Treatment

6.1. Limited

Defined as having nodal disease, with or without minimal local extension into nearby tissues, on one side of the diaphragm (Ann Arbor stage I or II), absence of B symptoms, no single tumour mass greater than 10 cm in largest diameter and normal ESR. Three groups have reported the results based on the use of brief exposure to ABVD followed by irradiation for clinical stage IA or IIA non-bulky HL [47], [48] and [49]. The results from these studies favour this approach in minimising the risks for later infertility, premature menopause, leukaemia as well as cardiopulmonary toxicity [50] and [51].

Further reduction in sequelae is possible by avoiding radiotherapy. This step is based on the National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group [52] trial comparing ABVD alone with either wide-field radiation for patients with favourable prognostic factors or two cycles followed by similar radiotherapy for those in the category with modest but statistically significant difference in progression-free survival in favour of combined modality therapy but no difference in overall survival.

Therefore such a regimen is currently regarded as an acceptable option for these cases in contrast to bulky early stage disease where additional irradiation remains the standard of care.

6.2. Advanced

Here chemotherapy alone has emerged as optimum [50] and [51]. Specifically protocol ABVD given on schedule, without delay and no growth factor support regardless of the absolute neutrophil count on the day of treatment, is advocated. Of note, however, is the use of stimulatory peptide increases bleomycin induced lung toxicity [53] and [54]. Alternatives are Stanford V and escalated BEACOPP [55] and [56] where encouraging results are offset by a marked increase in both short- and long-term toxicities, including infertility, infectious complications and second malignancies so that there is a relevance to use BEACOPP routinely.

However, it does represent a reasonable alternative particularly with high-risk disease as defined by the International Prognostic Score (IPS) [56] and [57]. Despite the CD20 negative immunophenotype in most of the cases several investigators have studied the role of rituximab in the treatment of classical variants. The basis includes direct killing of the Reed-Sternberg cells in

the 15% of these cases, depleting B cells in the microenvironment that may be necessary for tumour cell survival and the possibility that these may identify a postulated Hodgkin stem cell [58] and [59].

In the light of evolving experience are trials testing the impact of positivity on the interim PET CT scan in which early inclusion of BEACOPP or ICE containing ifosfamide, carboplatin, etoposide, with or without the use of stem cell transplantation, are attractive but there is currently no proof that this will improve outcome.

6.3. Relapse

Recurrence reduces long-term disease-free survival with standard dose chemotherapy to below 20% [60] and [61]. Exception exists in two subgroups. Firstly those who recur exclusively in the originally involved but unirradiated lymph nodes without B symptoms or extranodal disease [62] and [63] and here wide-field irradiation with or without additional chemotherapy may cure approximately 50% of patients [63] and [64]. Secondly when this occurs more than 1 year after remission and in the absence of constitutional symptoms repeating the same regimen or using potentially non-cross-resistant chemotherapy with or without irradiation eradicates disease in approximately 35% of the relapsed patients [60], [65] and [66].

However, both subgroups could be alternatively considered for autologous stem cell transplantation (ASCT). Immunomodulatory agents such as thalidomide or lenalidomide are generally well tolerated and thought to alter the inflammatory environment surrounding the Reed-Sternberg cells or by blocking angiogenesis. Thalidomide, in combination with vinblastine, had a response rate of 36% in a phase II study of heavily pre-treated patients with Hodgkin lymphoma [67]. Rituximab has documented activity in previously untreated and relapsed lymphocyte predominant Hodgkin lymphoma was shown by the GHSG [68].

In relapse 15 patients treated with four weekly doses of rituximab to achieve a response rate of 94% with a median time-to-progression of 33 months and a 7-year *overall survival* of 93%. The results of two randomised trials led to the establishment of autologous stem cell transplantation as the standard of care for relapses [69]. Presently no survival benefit could be established when employed in first or second relapse so favouring early use to minimize drug exposure and toxicity of previous salvage regimens.

Furthermore, such timing decreases the chance of an inadequate stem cell harvest. Approximately 50% with chemosensitive relapse, defined as a partial remission or complete remission to salvage therapy, will have a durable remission following this intervention as compared to 20% with stable disease or a minor response to salvage chemotherapy [69], [70] and [71]. To date no randomised trials have compared the effectiveness of salvage regimens. Thus etoposide with high-dose cytarabine and cisplatin – ESHAP, ICE, mini-BCNU or etoposide, cytosine arabinoside, and melphalan – BEAM, have been used. Recently gemcitabine-containing regimens have shown high response rates with an acceptable side-effect profile [72] and [73].

6.4. Long-term complications

Over time survival following treatment for Hodgkin's lymphoma has improved significantly [74], [75], [76] and [77] as a consequence of multiagent chemotherapy strategies, more accurate radiotherapy modalities as well as better inclusive management. This is offset by increased risk for developing second primary cancers, infections and cardiovascular disease [78], [79], [80] and [81]. The main cause of death remains disease itself but after 20 years this is negligible [82]. In contrast the relative risks from second primary cancers and cardiovascular disease continue to increase after 10 years.

More than 30 years following diagnosis this pattern is evident especially in those patients treated before the age of 21 but these risks seemed to decrease with age. Emergence of secondary acute leukaemia is strongly associated with the use of alkylating chemotherapy as well as mechlorethamine, which is one component of the MOPP regimen [50]. Since these regimens, having poor survival [79] and [83], are less used there has been fall in the incidence of this late effect [83] and [84]. Splenectomy did not show any increased risk of death arising from infections. One explanation could be that this is due to vaccination against pneumococcal infections usually administered before or immediately after this operation. Instructions on the correct use of antibiotic prophylaxis and treatment are accordingly strongly recommended.

Conversely protracted immunosuppression has been noted after splenectomy combined with radiotherapy and chemotherapy [85] and [86]. Smoking should be discontinued since it was shown to act synergistically with irradiation in the development of lung cancers and cardiovascular disease [87]. Especially in patients who received mediastinal radiotherapy screening for coronary artery disease, beginning 5 years after therapy, is recommended. Standard management of other risk factors including those for premature vascular disease, hypertension or lipid control may help to reduce this absolute excess risk.

6.5. Management during pregnancy

Since the vast majority of patients are treated with chemotherapy it is mandatory that staging of a pregnant patient should, besides necessary imaging, consist of a thorough history, physical examination, routine blood tests and a bone marrow biopsy. Examinations such as ultrasonography, chest X-rays with proper shielding or magnetic resonance imaging should provide the desired diagnostic information without increasing the risk of foetal malformation [88] and [89]. Abdominal or pelvic CT are safest avoided during pregnancy giving higher foetal radiation exposure of up to 0.02 Gy.

Positron emission tomography is increasingly favoured in staging. Since ^{18}F -FDG or radioglucose can cross the placenta and reach the foetus, it may involve higher radiation exposure than regular CT and its use can therefore not be recommended in this context [90]. However, it can be performed after delivery to assess treatment response with the caveat that breastfeeding should be discontinued for at least 24 h because this isotope is concentrated both in the breasts and milk [91]. Many cytotoxic agents cross the human placenta and reach the foetus [92] due to their relatively low molecular weight.

When treating with chemotherapy the physiological changes occurring during pregnancy such as the renal clearance of drugs or increased plasma volume must be considered [93]. These changes might decrease the level of active drug concentrations [93]. Exposure in the first trimester has been associated with a 20% risk of developing major malformations [92] with this risk being lower with single agents compared to combination regimens accordingly [94] and [95]. If unavoidable in this period, abortion should be considered.

Should termination be unacceptable, for religious reasons, one approach is to initiate single-agent anthracycline or vinca-alkaloid followed by combinations at start of second trimester. A further consideration is that alkylating agents may be less teratogenic than antimetabolites, which are considered to be the most injurious of all cytotoxic drugs used [92], [94] and [95]. There is some evidence suggesting that the ABVD combining adriamycin, bleomycin, vinblastine, dacarbazine is safe during pregnancy [93] and [96] as based on case reports. There is only limited experience regarding effects of MOPP [97] and none with the Stanford V or BEACOPP used in high-risk individuals.

Thus upon diagnosis induction should be initiated promptly with thought given to therapeutic abortion acknowledging potential teratogenic effects in the first trimester as treatment delay has shown to adversely affect survival [98]. Thereafter such intervention is usually not associated with malformations but has shown to increase the risk of foetal or neonatal death, pre-term delivery and low birth weight [92] and [99]. Women can be safely treated comparably to their non-pregnant counterparts [92], [93] and [96] with full doses given [92], [96] and [98].

Exposure to radiotherapy also needs consideration based on size of radiation fields and target dose. Since the most common presentation is supra-diaphragmatic lymphadenopathy, irradiation is feasible in early stage having isolated involvement of neck or axillary lymph nodes [100]. This modality in later gestation correlates with a carcinogenic effect and increased risk for leukaemogenesis or solid tumours within the first decade of life [101]. So far no teratogenic effects have been proven when granulocyte colony-stimulating factor or erythropoietin was needed to overcome treatment related cytopenia [102].

6.6. The cART era

Before the introduction of these regimens, median survival of HIV-HL patients was 1.5 years [103] and [104] and so, very clearly, effective intervention is statistically of significant benefit. While the incidence of HIV-HL has increased concurrently with these therapies outcome has improved dramatically, particularly in cases treated concomitantly with chemotherapy and anti-retroviral agents [34], [105], [106] and [107]. For example in a study by Gerard et al. [107] a significant increase in disease-free survival of 78% compared to 61% could be demonstrated.

Similarly in 57 HIV-related HL patients the impact of cART on outcome was tested on survival to different anti-lymphoma schedules [106]. Those who responded by increasing CD4 cell count of 100/ul or a RNA level below 500 copies/ml had an overall survival rate of 89% at 2 years compared with 44% for those who did not meet this criterion or were over 45 years of age [106]. Interestingly, limited data on the treatment with ABVD combined with cART in HIV-related HL, the standard in the non-immunosuppressed population, are available [106], [108] and [109].

For example the Spanish GESIDA/GELCAB Group [108] analysed outcome in advanced stage where 87% achieved CR: at median follow-up of 39 and 47 months, 5-year EFS and OS probabilities were 71% and 76%, respectively. An immunological response was observed in 56% and this was also virological in 68% of all treated patients leading to the conclusion that this regimen is effective and tolerated well. Also that immunosuppressed people should be treated like immunocompetent patients assume adequate support and infectious prophylaxis in the former. One possible explanation for the favourable impact on response and survival to cART is that control of viral replication might decrease the continuous activation of the lymphoid system, which is one of the features involved in AIDS-related lymphomagenesis [110].

Since the introduction of cART, commonly used chemotherapy regimens such as BEACOPP [111], Stanford V [112] or VEBEP [113] given concurrently, have yielded encouraging results and all have proven to be feasible and highly effective in this interesting category of lymphoma. When using BEACOPP an overall survival of 83% was seen at 2 years. With the Stanford V regimen 3-year OS, disease-free survival and freedom from progression being 51%, 68% and 60%, respectively. Although 69% of patients were able to complete the treatment without compromising dose intensity grade 3 or 4 neutropenia occurred in 78% despite the use of G-CSF and some neurotoxicity was noted.

In a separate analysis [114] based on the International Prognostic Score originally developed for Hodgkins [115] it was found that patients with high scores of greater than 2 treated with the Stanford V regimen did significantly worse showing a complete response (CR) of 67% compared to those with scores below 2 where CR was 100%. Also overall survivals were, respectively, 33% compared to 76% at 3 years thereby emphasising the favourable predictive value of low scores less than two.

The VEBEP made up of Vinorelbine, Epirubicin, Bleomycin, Cyclophosphamide and Prednisone study [113], demonstrated a high 75% complete remission, low relapse rate of 10% and outstanding overall and disease-free survival probabilities, respectively, of 86% and 90% at 2 years on the background of acceptable and moderate toxicity. The BEACOPP regimen so strongly advocated by the German Hodgkin Study Group seems to be highly effective but at the cost of some increased toxicity [111]. In a study of 12 patients only five received concomitant anti-retroviral therapy.

After the completion of six cycles of this regimen nine patients have remained in CR after a follow up period of 49 months but three patients died within the study period. Two of opportunistic infections during treatment and one to relapse after 2 years. The most commonly observed toxicity was bone marrow suppression as grade 3–4 neutropenia in 75% of the cohort. Notably plasma levels of retroviral copies increased only moderately or even declined during chemotherapy if cART was given concomitantly.

In a randomised trial full or dose-reduced schedules of epirubicin, bleomycin and vinblastine, together with zidovudine given from the beginning of therapy or started after the third cycle [116], gave an overall survival comparable for both arms but with the rate of opportunistic infection significantly lower in the dose-reduced treatment group. In a prospective non-randomised trial adding prednisone to EBV to this regimen with zidovudine or dideoxinosyne as anti-retroviral treatment together with G-CSF 74% of the patients achieved CR. Unfortunately

the relapse rate was 38% and median survival was 16 months, with *overall survival* probability of 32% and disease-free survival at 53% at 36 months [117].

The optimal chemotherapy for this viral – lymphoproliferative complex has yet to be defined. Despite the success achieved with the concomitant use of cART, there are also downsides, including drug-related adverse events and the development of resistance [118]. This has led to the view that therapy is best delayed until the CD4 cell count drops below 350/ μ l [119]. Significant complications of HIV infection usually occur when the CD4 cell count declines to less than 200/ μ l thus giving rise to the development of opportunistic infections [120].

Newer anti-retroviral regimens with more favourable toxicity and resistance profiles than prior regimens have led to the suggestion of initiating therapy at higher CD4 cell counts [121]. Another important question that needs to be determined is whether earlier introduction directed against the retrovirus at a CD4 cell count above 350/ μ l would prevent Hodgkin lymphoma is currently unclear. The strong association between these tumours and EBV infection in HIV-positive individuals [24], [32], [33] and [35] suggests that maintenance of higher CD4 counts might suppress the formation of EBV-containing malignant Hodgkin Reed-Sternberg cells.

There are several questions that should be addressed in the future. Up to date, there have been no prospective longitudinal studies assessing the optimal CD4 count at which initiation of therapy would be most beneficial. Furthermore, against this background of treatment outcome shown over the previous years the question arises whether Hodgkin lymphoma should now be elevated to the status of an AIDS-defining entity similar to certain other lymphomas and Kaposi sarcoma.

7. Concluding comments

Whereas the incidence of AIDS-related neoplasms have decreased over time, others tumours, referred to as non-AIDS-defining malignancies such as Hodgkin lymphoma (HL), invasive anal carcinoma, cancer of lung or skin have emerged thus challenging HIV-treating clinicians and including all subspecialties. With the introduction of cART over the past decade the focus was predominantly on AIDS related malignancies resulting in a reduction of incidence for Kaposi's sarcoma and non-Hodgkin lymphoma but neglecting certain tumours currently summarized as non-AIDS defining.

In the upcoming years research might profitably focus on some of these non-AIDS defining entities and especially HL which has up to date not been considered as meeting such criteria. Although there is conflicting literature some more recent studies suggest that retrovirally infected individuals are at higher risk for a variety of cancers independent from their CD4 count. There is meanwhile a considerable amount of data demonstrating that the immunosuppression associated with this agent places infected individuals at higher risk for developing lymphomas, Kaposi sarcoma, and cervical cancer.

Some data [30] and [122] suggests that non-AIDS-defining cancers are not associated with a low CD4 count per se and other factors, in combination with presence of the human immunodeficiency virus, such as coinfection with oncogenic agents (HHV8, EBV, HPV), lifestyle or advanced aging may be significant and seem to contribute to the increased risk for a range of neoplasms in this population.

This applies especially to HL occurring with a significantly, similar to AIDS related cancers, increased risk in HIV-infected individuals when compared with the general population. Specific therapeutic recommendations are lacking for these newly emerging malignancies including this particular lymphoma as well as others non-AIDS defining entities. One of the many urgent questions to be addressed in future is when should therapy be started and, if it was initiated sooner, would the effects decrease the risk of developing non-AIDS-defining malignancies or have an effect on their course?

There is substantial interest to re-evaluate the criteria for best time to first give these drugs on the background of publications. A few studies suggest that maintaining a higher CD4 count and lower HIV RNA level may have some protective effect on non-AIDS-defining cancer. However, there is more and more evidence that with rising CD4 counts the incidence of HL increases in HIV-infected patients whereas the incidence of NHLs decreases. Only few reports have documented the protective effects of anti-retroviral therapy in non-AIDS-defining cancers and no prospective studies have been yet performed.

The only one has so far showed that these were protective and that predictors for the development of apparently unrelated cancers were longer duration of the infection as well as a history of opportunistic events [30]. Interestingly CD4 count below 200/ul at the time of diagnosis was not associated with an increased risk for these entities, suggesting that factors other than a low CD4 cell count may be playing a role in the onset of cancer. In addition, patients not receiving medication or demonstrating higher viral copies were at greater risk for these cancers in general [30].

In contrast, another large linked population based study [122] has shown that other than Hodgkin disease, lung cancer, and testicular seminoma, neoplasms were not strongly associated with the development of immunosuppression. In patients with advanced stage Hodgkin in this setting, treatment with ABVD together with cART is feasible and effective. This supports the concept that patients where the lymphoma is present with virus should be similarly treated as immunocompetent cases presuming only that adequate supportive therapy and anti-infectious prophylaxis are given concomitantly.

Several important questions remain to be clarified in the future. Protocols and clinical trials should focus on certain non-AIDS defining malignancies such as HL which share many common features with the AIDS defining entities. This specific lymphoma could arguably now be considered as AIDS defining with the important caveat that research focus in the future be on how to improve survival and treatment outcome.

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