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Anti-Tumor Treatment

Systematic review of combination therapies for mycosis fungoides

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ABSTRACT

Background: A variety of therapeutic options are available for mycosis fungoides, the most prevalent subtype of cutaneous T cell lymphomas, but thus far, no regimen has been proven to be curative. A combination of treatments is a well-established strategy to increase the therapeutic efficacy. However, data from clinical trials analyzing such combinations for the treatment of mycosis fungoides are scarce.
Objective: To analyze the available evidence on combination therapies with emphasis on the combination of psoralen with UVA phototherapy (PUVA), interferon-alpha and bexarotene with another treatment.
Methods: Systematic literature review of the databases Embase, Cochrane, Medline, and Medline in Process.
Results: Combination of PUVA with interferon-alpha or retinoids did not result in an increased overall response rate. Addition of methotrexate but not retinoids to interferon-alpha may increase the overall response rate. Bexarotene was investigated in one trial each with vorinostat, methotrexate or gemcitabine, whereby only methotrexate possibly enhanced the effect of bexarotene.
Conclusion: For mycosis fungoides, no combination treatment has been demonstrated to be superior to monotherapy. Based on our analysis, we conclude that in certain clinical situations, patients may benefit from a combination of PUVA with interferon-alpha or a retinoid or a combination of the latter two. Furthermore, patients in advanced stages may benefit from the combination of methotrexate and interferon-alpha or bexarotene. Finally, the combination of bexarotene with either vorinostat or gemcitabine did not increase the overall response rate but resulted in more pronounced side effects and cannot be recommended.

Introduction

Mycosis fungoides (MF) is the most prevalent subtype in the group of primary cutaneous T cell lymphomas (CTCL). MF presents mostly with eczema-like patches to infiltrated plaques, featuring a good prognosis with a 5-year survival rate of 73–96% [1]. However, in the presence of cutaneous tumors, erythroderma as well as lymph node or organ involvement, the prognosis is less favorable with a 5-year survival rate of 27–44% [2]. Due to these prognostic differences, guidelines recommend different therapeutic regimens according to the clinical picture and stage of disease [3–4]. Among the most common recommended treatments are photochemotherapy with UVA (PUVA), interferon-alpha (IFNa) and retinoids. PUVA is often recommended for patch- and plaque-stage MF, while interferon-alpha, which has been first described in the treatment of MF in 1986 [5,6], is recommended alone or in combinations across all stages of MF [3,4,7–9]. Retinoids were introduced in the treatment of MF in the 1980s and were developed further during the following years to increase efficacy and reduce side effects [10]. Due to this fact, several retinoids such as etretinate, isotretinoin and acitretin were tested for their efficacy in the treatment of MF. In 1999, the US Food and Drug Administration approved the retinoid bexarotene, which has also been called a rexinoid as it binds to the retinoid X receptor, for use in CTCL [11,12]. Besides these three treatments, a wide range of other therapeutic options exist. However, long lasting remissions are rarely achieved in MF. Furthermore, patients in advanced stages of MF often do not respond satisfactorily to therapy and remissions tend to last only for several months [13]. To overcome these shortcomings, several combination treatments have been proposed and tested for CTCL [14]. The interpretation of the results from these trials is often difficult as the classification of CTCL has been revised several times during the recent decades. In a number

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of trials, CTCL entities were not distinctly reported and differentiated, so that patients with different types of CTCL, with a different biological behavior and prognosis, may have been treated and evaluated together in a trial. This strongly limits data extraction with respect to todays WHO-EORTC classification of cutaneous lymphomas.

The investigation of drug combinations in cancer treatment ideally fulfills several criteria: Single drugs should have been proven to be efficient, preclinical data should confirm synergism of both drugs, a combination of two drugs should be evaluated for the maximal tolerated dose and the efficacy of a drug combination should be analyzed in a randomized controlled clinical trial [15]. However, only very few combination treatment options comply with these criteria. We systematically reviewed three databases for reports on combinations of two systemic treatments. The results are summarized here with a special focus on the questions (a) if the addition of a second drug to a commonly used treatment option, e.g. interferon-alpha, retinoids or PUVA, offers an advantage to monotherapy and (b) if such treatment regimens have an acceptable profile regarding adverse events.

Methods

Search strategy

The databases Embase, Cochrane, Medline, and Medline in Process were searched from the start of the databases until December 2013. The search terms included cutaneous T cell lymphoma and mycosis fungoides as diagnoses in combination with a list of therapeutics (interferon, bexaroten, acitretin, retinoid, etretinate, gemcitabine, pegylated doxorubicin, methotrexate, chlorambucil, puva, chemotherapy, denileukin diftitox, vorinostat, cladribine, CHOP, alemtuzumab, fludarabin, pentostatin and combinations thereof) for articles in English or German language. The therapeutic drug list based primarily on above mentioned treatment guidelines [3,4,7–9] and was complemented by the experience of the authors. After the elimination of duplicates, this search retrieved 3060 results in total (first result with duplicates 4018). Abstracts were screened for suitable content independently by two investigators. Case reports were excluded from the further analysis. Any discrepancies were resolved by discussions. Fifty-three potentially relevant articles and abstracts were identified. These were assessed with regard to the following inclusion criteria: (a) At least 5 patients were included in the trials, (b) at least 70% of the study cohort were patients suffering from MF, and (c) information of overall response rate (ORR) was available. If the percentage of MF patients was not clearly indicated, the corresponding author was contacted with the question if at least 70% of the included patients had MF. Study results were included in the case of a positive answer and excluded in case of a negative answer or no reply. Twenty-eight trials were included in the analysis (Table 1), 25 trials were excluded (supplementary Table 1). We stratified the included patients with regard to their prognosis, i.e. the good prognosis group included patients with only cutaneous disease presenting as patches and plaques, whereas a poor prognosis encompassed stages with cutaneous tumors, erythroderma, lymph node or visceral involvement [1]. The evidence level of the included trials was graded according to published criteria [16]. For comparison of the therapeutic regimens, the mean and standard deviation for the rate of overall response, complete and partial remission was calculated. The rate of CR and PR for every single trial was extracted as given in the publications. As definitions of response differed slightly in between trials, the criteria for CR and PR are summarized in Table 1. Differences of response rates were tested for significance using the student's t-test where appropriate. As most studies were non-controlled trials, data for the ORR of a monotherapy were deduced from included controlled trials and respective monotherapy trials, which were identified by a Medline search.

Results

Combinations with PUVA

PUVA and interferon-alpha

Altogether, 11 trials investigated the combination of PUVA and interferon-alpha (IFNa) [17–27]. Most trials analyzed interferon-alpha 2a or 2b, and one trial reported results from treatment with pegylated IFNa. Three studies were randomized controlled trials (RCT), 3 prospective cohort studies, 2 retrospective case series, and 2 trials did not specify the way of data acquisition. One abstract included results from a retrospective analysis as well as a prospective randomized trial [24]. All trials nearly exclusively included patients with disease limited to the skin and the large majority of patients was characterized by a good prognosis. Two RCTs failed to demonstrate a significant difference between PUVA treatment alone and the combination therapy [26,27]. The ORR of the combination of PUVA and IFNa was within the range from 50 to 100%. The results of the analyzed trials, which reported rate for overall response, complete and partial remissions were homogenous as demonstrated by a mean ORR of 79 ± 16% (Fig. 1a). The tolerability of the combination was judged to be good by most authors. However, due to differences in the treatment schedules and application routes a comparison of the adverse events in different trials is difficult. In general it can be stated that the higher the dosage of IFNa, the more severe side effects were reported. Further trial details are summarized in Table 1.

PUVA and retinoids

We identified six trials in which isotretinoin, etretinate, or bexarotene were combined with PUVA [28–33]. We included 2 controlled trials, 1 prospective cohort study, 2 retrospective case series and 1 trial without a detailed specification. All trials mostly included patients with disease limited to the skin and a good prognosis. Both controlled trials failed to demonstrate a significant difference between PUVA monotherapy and the combination with either etretinate [31] or bexarotene [29]. All 6 trials showed consistent results with regard to the ORR (Table 1, Fig. 1a). The combinations were generally reported to be tolerated well with an acceptable side effect profile, mostly consisting of adverse events well known from retinoid monotherapy, e.g. hyperlipidemia, hypothyroidism and skin dryness. Further trial details are summarized in Table 1.

Combinations with interferon-alpha

IFNa and retinoids

Five trials investigated the combination of IFNa and a retinoid, i.e. acitretin, etretinate or isotretinoin [17,34–37] Of the 5 trials, one was a RCT and one a non-randomized controlled trial, while the remaining trials were cohort studies. Although the large majority of patients had skin-limited disease, one third of the patients had a poor prognosis. The combination of IFNa and retinoids was superior to IFNa monotherapy in the trial of Thestrup et al. [36]. Even more effective than IFNa plus acitretin was the combination of IFNa and PUVA [17]. The rate of overall response and complete remissions (CR) for combination treatment ranged from 42–80% and 20–54%, respectively. The tolerability of the combination was good in 4 trials, and patients exhibited adverse events usually known from IFNa monotherapy, e.g. flu-like symptoms and psychological side effects. In one trial, IFNa doses up to 36 x 10^6 IU