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Campath-1H treatment of multiple sclerosis: lessons from the bedside for the bench

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1. Introduction

Most therapies in modern medicine have been discovered by serendipity. But there is a growing strand of medicines that have emerged from basic science into the clinic through rational design. One such is Campath-1H. The technology to produce industrial quantities of monoclonal antibodies was developed in the early 1970s by Kohler and Milstein in Cambridge [1]. One of Milstein's students, Herman Waldmann, set about finding a rat monoclonal antibody that would lyse human lymphocytes and so treat lymphocytic malignancies. He developed the Campath-1 (from "Cambridge Pathology" department) series of antibodies. These were amongst the first monoclonal antibodies to be "humanised" by Greg Winter, another Cambridge academician, this process reduces the chances that patients mount an immune response against the therapeutic antibody [2]. So Campath-1″H″ was born. It targets the CD52 antigen present on all lymphocytes and monocytes and causes sustained depletion of T-cells. It has recently been licensed by the FDA and EMEA as a treatment for fludarabine-resistant CLL. But over the last 15 years or so, it has been trialled in transplantation and autoimmune conditions [3–11].

In 1991, we started to treat multiple sclerosis (MS) using Campath-1H. Our hope was that the T-cell repertoire regenerated after lymphocyte depletion by Campath-1H would exclude the aberrant autoimmune responses underlying MS. We proceeded with caution, treating one patient in 1991, six more during 1993 [12] and a total of 36 up to 1999 [13], all had SPMSs with Kurtzke scores of 6.0 or less at the time of entry into an MRI screening programme during which one gadolinium-enhancing lesion had to be present in the three months before patients were treated electively. The lessons learned from that cohort led to a change in strategy and we have since treated 22 patients earlier in the disease with activity confined to RRMS and before onset of the secondary progressive phase. Here we show how understanding the effects of this prototypical "bench to bedside" therapy have revealed aspects of the pathogenesis of MS sending us back to the bench.

2. Methods

We treated two cohorts of patients with MS, a "progressive" and a "relapsing" group. The progressive cohort consisted of 36 patients (22 women) with SPMS defined as a period of sustained increase in disability unaccompanied by identifiable relapses but following an earlier period of episodes with full or partial recovery. At the time of treatment, disease duration was 11.2 years (S.D. ±6.1 years) of which 3.6 years (±2.6 years) had been in the progressive phase, and mean EDSS was 5.8 (±0.8, range 3.5–7.0). One selection criterion for treatment was an increase in disability in the year before treatment of at least one EDSS point, during which annual relapse rate was shown to be 0.7 patient per year. Seven patients in this cohort received a second dose of Campath-1H, 2–4 years after the first treatment. The relapsing group consisted of 22 patients (17 women) with active RRMS. They received Campath-1H, either following the failure of licensed treatments to control their disease or because a high relapse rate early in the disease raised the prospect of a poor prognosis. Disease duration ranged from 9 months to 12 years (mean 2.7 ± 2.9 years) before elective treatment with Campath-1H, at which time mean EDSS was

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4.8 (±2.0, range 1.0–7.5). As a group, they had experienced a total of 133 relapses over 60 patient—years of combined disease history before treatment, giving an annual relapse rate of 2.2 per patient, this rose to 2.94 per patient in the immediate year before Campath-1H. This cohort included 17 drug-naïve patients in whom disease duration ranged from 9 to 41 months (mean 1.7 ± 0.9 years). During that time, the annualised relapse rate of this group was 2.8 per year, rising to 3.4 in the year before treatment, during which disability had increased by 0–7.5 (mean 2.1 ± 2.0) EDSS points. None of these patients had received concomitant therapy with any licensed or putative disease-modifying treatment for MS. Five additional patients had failed treatment with IFN-β. Their disease duration was necessarily longer ranging from 17 months to 12 years (mean 6.3 ± 4.9 years). Their increase in EDSS ranged from 0 to 5.5 (mean 2.4 ± 2.3) EDSS points in the previous year during which the relapse rate was 2.0 per patient. Patients were assessed every 3–6 months for the first 3 years after Campath-1H treatment and then annually, but with additional visits triggered by clinical events. A sustained increase in disability was defined as an increase in the EDSS of at least 1.0 point on consecutive examinations over 6 months, if the baseline EDSS was less than 6.0, or an increase of 0.5 point on consecutive examinations over 6 months, if the baseline was 6.0 or greater. The use of Campath-1H in this off-license study was approved by a local Ethics Committee (Cambridge LREC 02/315) and the United Kingdom Medicines Control Agency. Our early experience was with Campath-1H made by the Therapeutic Antibody Centre, Oxford.

We administered 100 mg of Campath-1H as five daily doses of 20 mg given intravenously over 4 h. Most patients were pre-medicated with IV methylprednisolone, 1 g over 1 h preceding the Campath-1H doses on days 1–3. Seven of 36 patients in the progressive cohort were re-treated with Campath-1H in order to maintain or increase perceived improvements. Subsequently, we offered elective re-treatment after 12–18 months giving a fixed total dose of 60 mg over three consecutive days (20 mg per day), again pre-medicated with corticosteroids, 9/22 of the acute relapsing group have now received a second course of Campath-1H. Patients in the progressive cohort were scanned intensively for the first 18 months after treatment, as previously described [14].

3. Results

The 58 patients treated to date have received a total of 74 courses of Campath-1H and have been followed prospectively for 280 patients—years. CD4 cells were depleted for a median of 61 months and CD8 cells for 30 months (19–46). B-cell numbers rose to 124% (S.D. ±74%) of pre-treatment levels at 27 (±15) months after treatment. In 13 patients, B-cell numbers had returned to baseline when last measured, at a mean of 62 (±17) months after treatment. However, in 18 patients, the most recent B-cell count, at 63 (±20) months, was still +66 (±48%) above baseline. These elevations in B-cell count rarely rose above the upper limit of the normal range. Those treated with Campath-1H alone experienced an acute cytokine response that we have described elsewhere [15], which is very significantly reduced by pre-treatment with corticosteroids. Seven infections that might represent adverse effects of Campath-1H have occurred, all were mild and none required hospitalisation: they included spirochaetal gingivitis (at 10 days), measles (at 11 days), herpes zoster (two instances, at 6 and 9 months, respectively), varicella zoster (at 2 years), recurrent aphthous mouth ulcers (from 6 to 9 months) and pyogenic granuloma (at 22 months). The principal adverse effect of Campath-1H therapy in patients with MS is Graves' disease [16]. One patient had experienced Graves' disease prior to Campath-1H treatment but to date, we have observed 15 new cases in the remaining 57 patients (27%), with one additional case of autoimmune hypothyroidism. Graves' disease developed within 5–21 months of the first treatment (14 patients) and 2 years after the second treatment (one patient). Ten of 15 cases were detected pre-symptomatically by screening for TSH. Three patients developed Graves' ophthalmopathy. This was transient in two cases. However, one of the 15/57 patients with Graves' disease has a permanent and cosmetically unpleasant ophthalmopathy, which has not threatened vision. All patients were initially managed using standard therapy for Graves' disease (carbimazole in the UK, the pro-drug of methimazole) for 6 months. Nine patients relapsed after treatment and received radioactive thyroid ablation.

In the SPMS cohort, Campath-1H reduced radiological evidence of disease activity, new lesions continued to form over 4 weeks but, thereafter, radiological markers of cerebral inflammation were suppressed maximally by >90% for at least 18 months and no new clinical relapses occurred. However, even during the first 18 months after treatment, dissociation emerged between the suppression of inflammation and disease progression [13] which has become even more apparent after longer follow-up. This cohort has now been observed for a total of 243 patient—years, giving an overall mean follow-up of 6.7 (S.D. ±2.1) years from treatment. Two patients have been lost to follow-up and three others have died (one suicide, one possible suicide and one death through sepsis in a severely disabled patient 7 years after Campath-1H). The remaining patients have been systematically followed by the same investigator for a mean of 7.6 years (±1.4 years, range 6.4–11.9 years). One year after Campath-1H, 33/36 patients in our progressive cohort had maintained their pre-treatment EDSS. With time, this proportion decreased, at last follow-up, only 4/36 had no sustained worsening of disability from their pre-treatment EDSS 7.5 years (±0.5) after treatment (7/36 if the more lax criterion for disability progression of just one EDSS point confirmed at 6 months throughout the EDSS is used). As a group, the mean rate of increase in disability after treatment was +0.2 EDSS points per patient per year, with a statis-

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tically significant reduced rate of progression compared to the year before treatment ($P < 0.001$), and a tendency for systematic reduction in the rate of disability acquisition. There was no difference in the rate at which disability accumulated between patients with early progression after treatment and those who were initially stable. Relapse rate, expected to decline as part of the natural history of MS in the secondary progressive phase, changed from 0.7 patient per year before treatment to an annualised rate of 0.02 patient per year, over the entire follow-up period of 243 patients per year, this group of 36 patients has experienced just six episodes, of which three occurred in the first 2 months after Campath-1H treatment, none have been associated with a persistent increase in disability.

Patients who had already progressed from baseline at the first follow-up interval (18 months) showed reduced brain volume at the time of initial treatment with Campath-1H by comparison with patients showing initial stability of clinical progression [13]. When 13 patients from this original cohort were re-examined 6 years after their last scan (which was itself 18 months after Campath-1H), there was no evidence for an increase in proton density or T1 lesion volume in the intervening period. However, 11/13 patients had evidence of further cerebral atrophy. The two with stable brain volumes were both amongst the group without atrophy in the first 18 months, however, one had shown significant progression of disability. The mean absolute change in cerebral volume was -1.37 (± 1.28) ml per year ($P = 0.002$). Five patients had new T2 lesions at follow-up and eight patients did not.

The RRMS cohort consisted of 17 drug-naïve patients and five who had failed licensed therapy, observed now for a mean of 19 months (range 6–74 months) after treatment, representing 32 patient—years of follow-up. Before treatment, their relapse rate was 2.21per patient per year (2.94 per patient in the immediate year preceding treatment). After treatment this cohort has had five confirmed episodes, giving a relapse rate of 0.14 and representing a 94% reduction in relapse rate. The extent of relapse rate reduction is the same if patients previously treated with IFN-ß are excluded, falling from 2.74 in the 28.5 patient—years before treatment (3.24 per patient in the immediate year before treatment) to 0.19 over the 26.3 patient—years of observation after treatment (93% reduction). Comparing, the accumulation of disability in the RR- and SPMS-groups in the year before treatment, the former showed a mean annual increase of +2.2 EDSS points. Mean annualised changes over the periods 0–6, 6–12 and 12–24 months were -2.4, -0.6 and -0.4 and $+0.2$, $+0.1$ and $+0.3$ for the RR- and SPMS-groups, respectively.

4. Discussion

This is the record of our total experience of the use of a humanised monoclonal antibody, Campath-1H, used to treat 58 patients since 1991. At first, we used this drug in patients with relatively advanced SPMS. Inflammation was suppressed but disease progression continued, suggesting the need for exposure to anti-inflammatory therapy earlier in the disease course. Despite adverse effects, we considered that safety data accumulated from this cohort were sufficiently encouraging to justify treating a group of patients with early clinically active MS.

Clinical and radiological data from our patients with SPMS suggest that just one or two pulses of Campath-1H significantly suppress cerebral inflammation for at least 6 years. Our 58 patients have together experienced only 11 episodes during 275 patient—years of follow-up during both the RR (32 years) and the SP (243 years) phases of the disease. There was no appreciable increase in the T1 hypointense, or proton density, lesion volume in a representative subgroup of patients with SP disease who agreed to an MRI scan some 6 years after treatment. However, there was evidence for progressive cerebral atrophy at a volume loss of +1.37 (± 1.28) ml per year. A similar dissociation between effective suppression of new lesions and continued cerebral atrophy in progressive patients has also been seen in a trial of the lymphocytoxic drug cladribine, a purine nucleoside analogue resistant to the action of adenosine deaminase [17,18] and of IFN-ß [19–21].

One interpretation of these observations is that axonal loss and inflammation are independent pathologies—an interpretation supported by epidemiological evidence that relapse rate during the progressive phase of MS does not alter disability outcomes [22]. If so, immunotherapy may not influence progression of disability, however, early it is deployed. However, several epidemiological studies have confirmed that relapse rate early in the course of the disease is associated with time to reach fixed disability milestones [23,24] and a relationship has also been reported between the load of early inflammatory lesions on MRI and later disability [25]. Patients in our SP cohort who progressed had more inflammatory load before treatment, confirming our belief that inflammation and axonal injury are intimately linked. Two processes account for axonal degeneration in the post-inflammatory phase: first, acutely transected axons undergo Wallerian degeneration over the subsequent 18 months [26], but this seems not to produce a progressive clinical deficit. Secondly, axons that escape injury in the acute phase may later degenerate through a non-inflammatory mechanism, dependent on prior inflammation. Specifically, we favour the interpretation that axon degeneration results from the loss of trophic support for neurons and axons normally provided by oligodendrocytes and myelin [27,28]. The influence of oligodendrocytes on axonal calibre and function is well described; oligodendrocytes myelinate axons, increase axonal stability and induce local accumulation and phosphorylation of neurofilaments within the axon [29–31]. Neuronal function is further influenced by oligodendrocyte-derived soluble factors that induce sodium channel clustering along axons, necessary for efficient saltatory conduction and maintain this clustering even in the absence of direct axon–glial contact [32]. We have shown that

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soluble factors produced by cells of the oligodendrocyte lineage support neuronal survival [33].

The lesson is clear. Once the cascade of events leading to tissue injury is established, effective suppression of inflammation does not limit brain atrophy or protect from clinical progression. It follows that there may only be an opportunity early in the disease course to suppress those components of the inflammatory process that initiate the cascade leading to loss of tissue integrity expressed as disease progression. This hypothesis is being tested in CAMMS223, a randomised single-blind trial comparing the efficacy of two doses of Campath-1H and IFN-β in the treatment of drug-naïve patients with early, active RRMS. The hope is that patients receiving effective anti-inflammatory treatment before the cascade of events leading to uncontrolled destruction of the axon–glial unit is irretrievably established will not subsequently accumulate disability, develop cerebral atrophy or enter the secondary progressive phase of the illness.

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