SUPPLEMENTARY INFORMATION:

CANCER IMMUNOLOGY, IMMUNOTHERAPY (SUBMITTED IN 2014) - ØYSTEIN BRUSERUD ET AL.

COMPARISON OF ECP TO OTHER TREATMENT OPTIONS - A DETAILED DISCUSSION OF THE CURRENT RECOMMENDATIONS FOR USE OF ECP IN THE TREATMENT OF GVHD

(Separate numbering of references)

Acute GVHD. Most clinical studies of ECP and of the pharmacological alternatives for second-line treatment are nonrandomized; many of these studies are relatively small and for each therapeutic alternative only a few studies are usually available (Supplementary Table) [1-38]. The survival data from representative ECP studies are compared in the table; one of these studies was a summary of previous Italian studies [7] and one was only a brief Letter to the Editor [8]; for these reasons they were not suitable for the more detailed presentation given in Table 1 of the article. Survival data for 9 ECP studies were suitable for this comparison; the 9 studies included a total of 257 patients, most of them are retrospective and both the response rates as well as the survival show a wide variation. Anti-thymocyte globulin is a therapeutic alternative that has been investigated in 5 studies [10-14]; 233 patients have been included and the response and survival rates are comparable to ECP but with less variation. The same is true for IL2 targeting therapy [15-18]; 135 patients have been included in 4 studies of either IL2 or IL2 receptor (CD25) targeting therapy. The experience with the other pharmacological alternatives is even less. It is not surprising that the available guidelines differ in their recommendations.

It can be seen from the Supplementary Table that the efficiency of mesenchymal stem cell therapy is comparable to alternative therapeutic strategies for the treatment of steroid-resistant acute GVHD [19-24]. The clinical studies of this therapeutic approach have included a relatively large number of

patients, the complete response rate is relatively high in several studies, the acute toxicity seems minimal and the general long-term immunosuppression is weak with low non-relapse mortality for responder patients. However, one study suggested that MSC treatment for acute GVHD can be associated with increased risk of late infections [39], but this was a small study and the observation has to be confirmed in additional studies (preferably randomized studies) before a final conclusion can be reached.

All the studies summarized in Table 1 emphasize the importance that both treatment efficiency and toxicity has to be carefully evaluated when comparing various therapeutic alternatives, and patients receiving long-term treatment for steroid-resistant GVHD have relatively high non-relapse mortality because these patients are severely immunocompromized. In this context ECP seems to have an advantage with a relatively low/absent general immunosuppressive effect. Three available guidelines are summarized below.

The British Society for Bone Marrow Transplantation. [41]. These guidelines emphasize the excellent safety profile of ECP. However, even though side effects appear to be mild and there are no reports of increased frequencies of infections or relapse, the authors conclude that the first line treatment should be steroids whereas ECP as well as anti-TNFα antibodies, mTOR inhibitors, mycophenolate mofetil and interleukin 2 receptor antibodies should only be used as second line treatment. The available knowledge does not allow any of these strategies to be preferred.

The American Society of Blood and Marrow Transplantation [42]. These guidelines distinguish between second line and further treatment, and they conclude that there is at present no support for the choice of any specific agent for second-line treatment of acute GVHD based on 6 months survival data, complete response rates or overall response rates. These guidelines also emphasize the limited toxicity, lack of significant interactions and no risk of viral reactivation as important advantages of ECP. These authors especially review and point to the advantage of low toxicity by ECP. The most important disadvantage is traveling to an ECP center, and similar to several other alternatives ECP is very expensive.

The Italian Group for Bone Marrow Transplantation [43]. This group also concludes that there is currently no evidence to suggest that ECP is superior to other second-line alternatives.

Chronic GVHD. The guidelines from the British Society for Bone Marrow Transplantation recommend steroids as the first-line treatment eventually in combination with a calcineurin inhibitor, and as a possible second line treatment they recommend ECP for skin, oral and liver GVHD [44]. Alternative second line options are rapamycin, pentostatin, rituximab (cutaneous and musculoskeletal chronic GVHD) and imatinib (pulmonary and sclerodermatous chronic GVHD). ECP, imatinib and rituximab are regarded as third line treatment when other organs are affected. A wide range of agents have been tried in small clinical studies, but mycophenolate mofetil, metotrexate and pulsed corticosteroids were the only additional third line therapies that were recommended. Inamoto and Flowers [45] recommended ECP as a second line treatment together with rituximab, imatinib, pentostatin, mesenchymal stem cells, mycophenolate mofetil and mTOR inhibitors. Both these reviews as well as the Italian Group for Bone Marrow Transplantation [43] concluded that it is not possible to recommend one specific strategy as the preferred second line treatment.

Supplementary table. A summary of representative clinical studies investigating the effects of various therapeutic alternatives in acute GVHD (numbering of references is the same as in the printed article).

REFS.	PATIENT NUMBER	TYPE OF STUDY	COMPLETE RESPONSE RATE	COMPLETE + PARTIAL RESPONSE RATE	SURVIVAL	TIME FOR SURVIVAL EVALUTAION
EXTRACORPOREAL PHOTOPHERESIS - IMMUNOMODULATION - 257 PATIENTS INCLUDED IN 10 RETROSPECTIVE STUDIES						
[1]	59	Prospective			0.47	Estimated 4 years survival
[2]	50	Retro		0.68	0.44	Median time to follow-up 14 months, range 2-102 months
[3]	41	Retro		0.73		
[4]	33	Prospective	0.54	0.21	0.69/0.12	Estimated 5 years survival for responders/nonresponders
[5]	23	Retro	0.52		0.48	Median survival after 37 months
[6]	15	Retro	0.73	1.0	0.85	2-years overall survival
[7]	12	Retro	0.59	0.83	0.67	Median observation time 16 months (range 1-56 months)
[8]	12	Retro	0.50	0.33	0.57	5 years overall survival
[9]	12	Retro		0.75		
ANTITHYMOCYTE GLOBULIN - T CELL DEPLETION - 233 PATIENTS INCLUDED IN 5 STUDIES (3 RETROSPECTIVE)						
[10]	79	Retro	0.20	0.54	0.44	6 months
[11]	58	Retro	0.07	0.28		6 months
[12]	47	Phase II	0.32	0.57	0.45	6 months
[13]	27	Phase II/III	0.33	0.56	0.55	6 months
[14]	22	Retro		0.18	0.61	6 months
BASILIXIMAB - chimeric IL2 receptor antagonist - ONE PHASE 2 STUDY INCLUDING 23 PATIENTS						
[15]	23	Phase II	0.17	0.83	0.55	6 months
DACLIZIMAB - anti-CD25 - 3 STUDIES INCLUDING 112 PATIENTS (1 RETROSPECTIVE)						
[16]	57	Retro	0.33	0.54	0.28	6 months
[17]	43	Phase II	0.37	0.51		6 months
[18]	12	Phase II	0.08	0.50	0.33	6 months

MESENCHYMAN STEM CELLS - IMMUNOMODULATION - 7 STUDIES INCLUDING 164 PATIENTS						
[19]	55	Phase II	0.57	0.75		Overall survival at 2 years 0.53 for responders and 0.16 for nonresponders
[20]	32	Phase II	0.77	0.16		
	12	Phase I/II	0.57	0.33	0.55	Overall survival after 30 months
[21]	10	Phase I/II	0.10	0.60		
[22]	8	Phase I/II	0.60	-		
[23]	37	Retro	0.65	0.87	0.37	Median followup 2.9 years
[24]	12	Phase I/II	0.58	0.75	0.41	Median followup 611 days
PENTOSTATIN - IMMUNOMODULATION - 4 STUDIES (3 RETROSPECTIVE) INCLUDING 109 PATIENTS						
[25]	15	Retro	0.13	0.33		
[26]	12	Retro	0.33	0.50		Median overall survival at 5 months
[27]	24	Retro		0.36	0.17	Followup at 2 years
[28]	58	Phase II		0.64	0.78/0.70	Overall survival evaluated after 1/2 years
MYCOPHENOLATE MOFETIL - IMMUNOSUPPRESSION - 4 RETROSPECTIVE STUDIES INCLUDING 98 PATIENTS						
[29]	48	Retro	0.31	0.79	0.47	6 months
[30]	27	Retro	0.26		0.52	6 months
[31]	13	Retro	0.15	0.46	0.66	6 months
[32]	10	Retro	0	0.60	0.77	6 months
DENILEUKINDIFTIOX - toxin-coupled anti-CD25 antibody - 2 PROSPECTIVE STUDIES INCLUDING 54 PATIENTS						
[33]	32	Phase I	0.38	0.53		6 months
[34]	22	Phase II	0.18	0.27		6 months
SIROLIMUS - mTOR inhibitor - ONE RETROSPECTIVE STUDY INCLUDING 34 PATIENTS						
[35]	34	Retro	0.4	0.76	0.48	6 months
INFLIXIMAB - anti-TNFα antibody -ONE RETROSPECTIVE STUDY INCLUDING 21 PATIENTS						
[36]	21	Retro	0.62	0.67	0.52	6 months

ETANERCEPT - soluble dimeric TNFα receptor 2 - ONE STUDY INCLUDING 13 PATIENTS						
[37]	13	Retro	0.38	0.46	0.77	6 months
METHOTREXATE - IMMUNOSUPPRESSION -ONE RETROSPECTIVE STUDY INCLUDING 12 PATIENTS						
[38]	12	Retro	0.42	0.58	0.58	6 months

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