Extracorporal hemodialysis with acute or decompensated chronic hepatic failure

Background

Acute liver failure (ALF) and acute-on-chronic liver failure are severe deteriorations of the liver function with relatively bad prognosis. About 20,000 persons are dying from these diseases per year in Germany. Characteristic complications are development of multiorgan failure, arterial hypotension, disseminated intravascular coagulation (DIC) and disorders of microcirculation leading to damage of extrahepatic organs.

Focus of the therapy of ALF and ACLF is the stabilisation of the liver function until an improvement of the symptoms by the self-regeneration of the liver has been achieved or until a suitable organ for liver transplantation is available (bridging to transplantation).

Conventional diagnostic procedures and therapy of ALF and ACLF focus on to identify triggering events and reasons of liver failure like virus infection, alcohol abuse or acute intoxication, and to avoid them. Further objectives are to prevent the development respectively the progression of secondary organ dysfunctions or organ failure (like heart or renal failure or cerebral complications).

Under certain circumstances a liver transplantation is an option for therapy of liver failure, but the main limiting factor is the availability of organs. In combination with the scarcity of organs, possibly leading to waiting times up to years, the initial health state and the progression of the disease are prognostic factors concerning a successful transplantation.

Most of the times the endocrinological function of the liver can at least partly be compensated, but the removal of toxins can only marginally be substituted by conventional conservative therapy. To improve this component of the liver function is the main objective of extracorporal liver support systems.

The following principles of liver support systems can be differentiated:

(i) Artificial, cell-free systems: classic dialysis, BioLogic-DT / -DTPF, SPAD, MARS, FPSA and Prometheus

(ii) Bioartificial systems based on liver cells: ELAD, HepatAssist, BAL, BLSS and MELD

(iii) Extracorporal liver perfusion systems: ECPL

This HTA report focuses on the first category, the artificial systems, because only these approaches currently are relevant in the German health care system. Until 2003 there was no regular reimbursement of artificial liver support technologies and the use of the systems was paid by industry financed studies or by the hospitals as part of their individual budgets. In 2004 a category “Extracorporal liver assist device” was introduced in the list of “additional payments” in the German DRG-system, which makes reimbursement for hospitals using the technology in inpatient care possible, based on an hospital’s individual contract with by German statutory sickness.
Objectives

To report the present published evidence and future research need on medical efficacy and economic effectiveness of extracorporeal liver support devices for treatment of patients with ALF or ACLF.

The evidence on medical efficacy is differentiated into the following questions:

1. Number and quality of systematic reviews and original primary studies?
2. Is it possible to demonstrate the medical efficacy of extracorporeal liver assist systems by results of randomized clinical trials?
3. Are there subgroups differences in efficacy of the technology?
4. What could be the objectives to use the technology?
5. Are there relevant side effects or complications?
6. What could be the indication for the use of the technology?
7. Is there a need for further research?

Methods

An extensive, systematic literature search in the following medical, economic, and HTA literature data bases was performed: MEDLINE, EMBASE, BIOSIS Previews, SCISEARCH, CATLINE, SOMED, AMED, Elsevier Biobase, IPA, Global Health, CAB, Biotechnobase and GEROLIT. Randomised and non-randomised controlled trials, systematic reviews including meta-analysis were identified and included in the further analysis. Further documents could be detected by systematically searching HTA databases like the Cochrane Library, as well as by systematically comparing the references of the identified publications, non-systematic review and relevant scientific books. The literature search was limited to publications edited between 1990 and the beginning of 2004.

Results

Overall 15 publications on the medical efficacy of extracorporeal liver assist devices were detected and included in the further analysis: Two short and one long HTA reports plus one update, two publications presenting the results of one systematic review and eleven publications presenting the results of controlled clinical trials on the use of MARS or Biologic-DT. No randomised controlled trial on the use of Prometheus could be identified and the technology was not included in one of the systematic reviews.

Six publications presented the results of four randomised controlled trials investigating the use of BioLogic-DT / DTPF. All four studies included patients with hepatic encephalopathy, but the study populations differed concerning the underlying aetiology of liver failure. In all four studies patients were randomised to an intervention group and a control group with standard therapy. There was no information on concealment, type of randomisation or a discussion of the possibility of a sham control or blinding. No study chose survival rate or survival probability as outcome parameter, although in three studies the survival rates could be extracted. All four studies included clinical scores as outcome parameter, but no study could demonstrate a significant change of the grade of hepatic encephalopathy or the neurological status. Concerning routine lab tests like blood counts or liver specific tests no significant advantage of the intervention group could be demonstrated. In contrast to this lack of significant results on efficacy some complications and side effects were described, although in these cases the question of causality has to remain unanswered. All studies were monocen-
tric and were performed at highly specialised university hospitals. The methodological limitations of all of the studies (e.g. small sample size, high drop-out rates, heterogeneous study population, short or no follow-up) strongly limit the scientific evidence and make it difficult to interpret the results at all.

Investigating the use of MARS five publications were identified presenting the results of five studies. Additionally the systematic reviews of the Swedish and French HTA agencies and two publications presenting the results of a Cochrane report were included. One of the studies included patients with ACL and a hepatic encephalopathy grade III - IV, the other four studies chose a population of ACLF patients of differing aetiologies. Three of the five studies were randomised; the other two had a non-randomised controlled design. All studies compared standard treatment with respectively without additional MARS treatment. Three studies present results on survival: In two randomised trials a significant improvement in 30d-survival after MARS treatment could be demonstrated; one study presented a clear but non-significant trend to a higher survival probability one year after treatment with MARS. One study showed a significantly better grade of hepatic encephalopathy in the MARS group compared to a worsening in the control group. All other publications do not present results on clinical scores. In two studies significant improvements of specific lab tests (creatinin and bilirubin) and in three studies of hemodynamic parameter (e.g. mean arterial pressure) are presented. Relevant side effects or complication were not reported. Two studies were bicentric, the other three studies were monocenter studies. All studies were conducted at highly specialized university hospitals. It has to be doubted that these results could be transferred to a broader routine use. Although the methodological quality of the studies was slightly better compared to the studies on BioLogic-DT / -DTPF the scientific evidence of the results is limited by small sample sizes (Max. twelve per group), highly selected study populations and short follow-up periods of maximum one year.

Concerning economic aspects only two publications on MARS could be detected at all. No publications on Prometheus or BioLogic-DT / -DTPF were identified. One publication presents a calculation of the possible effect of MARS on hospitalisation costs and calculates savings of 4,000 EUR per patient treated with MARS. The study shows major methodological mistakes that make it impossible to further interpret the results. The other study presents one-year results of a non-randomised clinical cohort-trial on survival, costs and cost-effectiveness of MARS treatment in patients with ACLF due to alcoholic liver disease. The study shows an incremental cost-effectiveness of 29,719 EUR per life year gained after one year from a payer's perspective (German statutory sickness fund, neglecting the intervention costs because of lacking reimbursement at this time), respectively 79,075 EUR per life year gained from a societal perspective. Including health related quality of life aspects the incremental costs per quality adjusted life year (QALY) gained were calculated to be 44,784 EUR from a payer's perspective respectively 119,162 EUR from a societal perspective. The authors state that prolonging the time horizon of the calculations would improve cost-effectiveness ratios. The limitations of the study design also create doubts concerning the scientific evidence of the results.

Conclusion

The results of the detected publications do not give any evidence for a positive medical efficacy of BioLogic-DT. Concerning MARS there is some evidence for positive effects on 30d-survival, clinical parameter, and some lab
tests, although the evidence is limited by the small number of studies and their methodological weakness. Clearly there is further need for randomised controlled trials with sufficient sample sizes and longer follow-up periods. Also the efficacy of artificial liver support systems for patients with ALF and for bridging to transplantation has to be demonstrated.

The currently strongly limited evidence shows a trend to an acceptable cost-effectiveness of MARS, although the results are based on only one non-randomised trial.

To give valid recommendations concerning the medical efficacy as well as the cost-effectiveness of artificial liver support systems further studies are necessary to demonstrate the value of the technologies for clearly defined indications over a longer time horizon concerning health-related quality of life, defined subgroups, complications and economic consequences.

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