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Composite tissue allotransplantation in Europe. Logistics and infrastructure of a centre

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Summary

Background: Composite Tissue Allotransplantation (CTA) is a new medical field of growing importance. This paper focuses on the infrastructure and organisation of European CTA centres and discusses the differences between national health systems.

Material/Methods: Eight European centres (Valencia, Innsbruck, Munich, Lyon, Amiens, Creteil, Wroclaw, Monza) were sent with a specially-designed, standardized, 20-item questionnaire.

Results: Five of the eight centres returned our questionnaire: Munich, Innsbruck, Lyon, Amiens, Wroclaw. Since 1998, CTA has been performed at these centres. In both French centres and the Polish centre public funding is available in addition to the coverage provided by health insurers. In Munich the costs for a double upper-arm transplantation were € 150,000 with an additional € 50,000–70,000 per year. In Lyon the costs for a singular hand transplantation were € 70,000 per year and in Wroclaw (Poland) the costs for a hand or upper arm transplantation were € 20,000–30,000. As many as 17 different medical professions are involved in the CTA at the different centres.

Conclusions: CTA is an innovative promising therapeutic tool that is based on the experiences of solid organ transplantation and profound microsurgical skills. Due to the complexity of the infrastructure, sourcing and the organisation CTA can only be successfully performed at specialized centres. A European network with an international European waiting list and a central coordination for CTA should be established. In order to advance CTA as an important tool in reconstructive surgery we must turn our attention to how the costs will be met, the legal environment for procurement of adequate donors and open ethical questions.

Key words: **CTA • comparison European centres • legal environments**

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BACKGROUND

Composite tissue allotransplantation (CTA) is an innovative operative therapy for complex soft tissue defects in selected cases [1–4].

CTA has an enormous potential to improve form and function and thereby quality of life for our patients [5].

Nevertheless, CTA in the clinical setting remains controversial even among experts because alternatives like prosthesis or plastic-surgical reconstructions do exist. Only 26% of plastic surgeons in North America [6] and 24% of North American hand surgeons are in favour of the CTA [7].

According to broad estimates, each year in the USA up to seven million patients could benefit from a CTA. These patients suffer from missing or inoperable limbs or tissue defects due to trauma and malformations or metabolic dysfunction [8].

The expected benefits of a CTA and the associated improvement in the quality of life have to weighed against the risks of the procedure, and the side effects of immunosupression [6,9] and these matters are constantly discussed among experts.

In order to gain the whole benefit, to manage the comprehensive follow up and to generate scientific results from the CTA, patients have to be treated exclusively at designated centres with a lot of experience in reconstructive microsurgery and plastic surgery and, especially, in transplantation medicine.

When carefully selecting the potential recipients of a CTA motivation, acceptance of the necessity of lifelong immunosuppressive treatment, and compliance to physiotherapy for the transplanted limb are of paramount importance.

Other important patient considerations are size, sex, colour of the skin, pattern of hair growth, constitution, age and immunologic matching of the donor and recipient.

For a successful CTA the forming of centres is also important in light of necessary intensive physiotherapy and psychological support.

To obtain the best possible result it is important that there be a close interdisciplinary cooperation between surgeons, physiotherapists and occupational therapists [10].

To coordinate the explantations and transplantations the European centres have to be linked and donor procurement has to be organised internationally. This is especially important because of the necessary matching of donor and recipient in terms of distinctive features.

The CTA centres have the prerequisite infrastructure including coordinators, 24-hours on call and international communications technology.

It is also important to restrict CTA to a few selected centres because these centres are all familiar with the need to match transplanted tissue both in terms of HLA compatibility and phenotypic features (especially in face transplantation) and this shared familiarity facilitates communication between them.

The first hand transplantation was performed in Ecuador in 1964 [11], but this hand had to be removed three weeks after the transplantation because of rejection [12]. Dubernard [13] operated the first successful hand transplantation in 1998 using immunosuppressive therapy but this hand had to be removed two years later due to poor patient compliance and a consecutive chronic rejection.

According to IRHCTT (International Registry on Hand and Composite Tissue Transplantation) the following transplantations have been performed at the time of submission to date:
– Twenty-two patients with single hand transplantation,
– Fourteen patients with double hand transplantation,
– Two patients with finger transplantation.

Additionally face, femur-diaphysis, knee, uterus, abdominal wall, larynx and lower extremity have been transplanted into 43 patients worldwide.

Hand transplantations were performed in Monza (Italy), Selayang (Malaysia), Louisville (USA), Guangzhoe (China), Lyon (France), Munich (Germany), Innsbruck (Austria), Wroclaw (Poland).

The legal environment for CTA in Germany is in need of modification. With the coming into force of Germany's Human Tissue Act on August 1st 2007 and the EU directive on matters related to human tissue and cells (EU 2004/23/EG) we wonder whether CTAs of faces and arms are on the same legal footing as solid organ

transplantations or tissue transplantations (i.e. Euro Skin Bank allograft tissue). In Germany arm and face transplantations seem to exist in a grey zone somewhere between solid organ transplantation and tissue transplantation [14]. In contrast in Poland, France and Austria the legal status of CTA is equivalent to solid organ transplantation.

European centres for CTA feature the specific interdisciplinary infrastructure and logistics needed to respond to increasing patient interest. Reconstructive surgeons whose patients ask them about the availability of CTA are surely interested in an up-to-date status report on the general infrastructure already in place as well as how the costs of CTAs are covered.

Material and Methods

Eight European centres (Valencia, Innsbruck, Munich, Lyon, Amiens, Creteil, Wroclaw, Monza) were contacted with a specially-designed, standardized questionnaire. The questionnaire was translated into English, Spanish and French. Five centres filled out and returned the questionnaire: Innsbruck, Munich, Lyon, Amiens, Wroclaw.

Based on the answers to 20 questions the structure of the centres was retrieved and compared. We enquired about the infrastructure with the number of transplantations performed in each centre, the number of the participating microsurgeons and medical professionals, the time intervals between follow-up check-ups of the patients and how many different medical specialists took part in these check-ups.

In addition to the legal environment and we also analysed how the costs of CTAs were covered by individual national health systems.

Results

Infrastructure

Since the first hand transplantation in 1998 in Lyon, 22 CTAs have been performed at the five European centres. In 2005, a partial-face transplant was performed the first time ever by Prof. B. Devauchelle, Amiens and Prof. Dr. J. M. Dubernard, Lyon. Eighteen forearms and hands (six CTAs in Innsbruck 2000–2006; nine CTAs in Lyon 1998–2008; three CTAs in Wroclaw 2006–2008) have been transplanted since then. In 2008, in Munich Prof. Biemer and his team transplanted both upper arms of a patient for the first time worldwide, at St. Jadwiga Hospital in Wroclaw in 2009 Prof. J. Jablecki transplanted a single upper arm [15,16].

The number of participating microsurgeons per CTA-team was five in Amiens, Lyon and Wroclaw and eight to ten in Innsbruck and Munich.

Many different medical professions are represented by the specialists at each CTA centre, reflecting the high logistic input of a CTA-centre.

The number of specialties represented by staff involved in CTA were given as follows: In Wroclaw 8, in Innsbruck 10, in Amiens 11, in Lyon 13 and in Munich 17. The individual specialisations consist of surgical sub-specialties such as plastic surgery, hand surgery, traumatology, transplantation surgery and face surgery. CTA centre staff also included anaesthetists, immunologists, oncologists, dermatologists, pathologists and radiologists as well as physiotherapists, nurses, medical ethics, psychologists and prosthesis engineers. None of the centres responding listed a staff member, such as a pastor, to attend to patients' spiritual needs.

Follow-up care

Follow-up care clearly reflects the interdisciplinary approach of a CTA. The follow-up care after a CTA described by all the respondents was both thorough and at short intervals, and was provided by transplantation surgeons, plastic surgeons, face surgeons, as well as immunologists, psychologists, oncologists and dermatologists. The follow-up intervals were similar at all the centres (Table 1).

The specific aspects of immunosuppression for CTA recipients are modified at the moment. A standardized postoperative immunologic monitoring consists of the following parameters: viral diagnostic CMV routinely, EBV, HSV and BK virus in case of a suspected infection, complete blood count, HbA1c.

The psychological follow up was similar at all the centres according to the above mentioned protocol (Table 2).

At none of the 5 centres does a surgeon from the CTA team contact the family of the donor to obtain informed consent.

Legal environment

In Germany the transplanted upper arm has a legal status equivalent "tissue"; in France, Poland

Table 1. Medical follow-up care at the different CTA-centres.

	1st year	2nd year	3rd year	4th year	5th year	From the 6th year
Weekly	x					
Monthly	x	x	X			
Quarterly		x	X	x		
Every 6 months			X	x	x	
Annually					X	X

Table 2. Psychological follow-up care at the different CTA-centres.

	1st year	2nd year	3rd year	4th year	5th year	From the 6th year
Weekly	x	x	x			
Monthly	x		x			
Quarterly	x	x				
Every 6 months		x	x	x	x	X
Annually			x	x	x	X

and Austria it is the legal equivalent of a "solid organ". In France, until 2005, there was a distinction drawn between "tissue" and "solid organ". Since 2005, vascularised composite tissue (i.e. face, arm, hand) is legally equivalent to vascularised solid organs (liver, heart, lungs). In contrast to that there is non-vascularised tissue like tissue from the Euro Skin Bank or elsewhere.

In Germany CTA is covered in the law on medicines, not by the law on transplantations, as is, for example, the transplantation of solid organs. In Austria, Poland and France CTA has a status legally equivalent to solid organ transplantation.

Costs

In Munich CTA is covered exclusively by health insurers. A dual mode of paying for these complex new therapies exists in France: a combination of health insurance and public funding. In France the government provided one million euros for the clinical research accompanying the first five CTA double-hand transplantations. Since the one million euros go for clinical research to support the first CTAs, in the future, health insurance will cover the costs of a CTA in France. For face transplantation it is quite similar in France: both centres involved (Amiens and Lyon) received € 250,000 as governmental aid for the first face CTAs to pay for accompanying clinical research. Other costs are being met by French health insurance.

In Poland a dual mode of paying for CTA exists which is very similar to the French system.

The costs for a CTA in Munich for the double upper-arm transplantation were € 150,000 plus an additional € 50,000–70,000 annually; in Lyon annual costs for a CTA-hand transplantation are € 70,000. The centre in Wroclaw stated that a hand transplantation costs € 20,000 and an upper arm transplantation € 30,000.

Discussion

Infrastructure

The data shows that a CTA can only be successfully performed at a centre with an interdisciplinary cooperation of up to 17 different medical professions involved in the CTA associated with a considerable degree of logistical challenges. Apart from that, an enormous amount of experience in reconstructive microsurgery as well as transplantation medicine and immunology are necessary [17]. The complete extensive follow-up care of complex patient needs requires highly qualified physiotherapists, occupational therapists and hand therapists as well as psychological counselling.

The whole infrastructure for a CTA is generating substantial costs so that in order to optimise the utilisation of resources all CTA-activities should be focused to designated centres.

Time and effort of a CTA-arm transplantation corresponds to solid organ transplantation (e.g.. liver transplantation) in terms of costs and organisation.

A European network with an international European waiting list and a central coordination office for CTA should be established in order to find matching donors for more patients on the waiting lists.

CTA broadens the options of modern transplantation medicine to save life or to improve quality of life by organ transplantation [5] when it is in the hands of innovative reconstructive plastic surgeons.

Legal environment

Differences relevant to CTA between the legal environments of the five national systems where the centres are located are striking.

In Germany the law regulating transplantation covers solid organ transplantation and the law on medicines covers composite tissue handling/transplantation. Dubernard told us that in France since the year 2005 there is a distinction between "organ", "vascularised tissue" and " (non-vascularised) tissue" (i.e. cryo-conserved skin). "Vascularised tissue" like a hand, a face or arm is legally equivalent to a solid organ. In Austria and Poland CTA is legally equivalent to solid organ transplantation.

Knobloch et al. [14] showed that because of existing definitions and the criteria for organ transplantation and tissue transplantation that there are no distinct assignments for CTA in the German law. Vascularised composite tissue is legally equivalent to "tissue" according to German law.

The tissue-medicine-complex may have a great impact on solid organ transplantation and the willingness of people to donate organs [18]. "It is not clear to medical doctors how they should address patients and families about the coexistence of altruistic organ donation and commercialized tissue medicine," says Dr. W. Puehler from the Federal Medical Association of Germany.

"Tissue donation is a legal minefield," says L. Herzog specialist solicitor for medical law from Hildesheim, Germany. The terms "tissue" and "tissue-donation" seem to be ambiguous in the population even though tissue-donation has been carried out for more than 100 years and over 10,000 tissues are transplanted in Germany each year.

We agree [19] with Siemionow [20] and Dubernard that vascularised composite tissue in terms of function, complexity and the necessary logistic effort has more similarities with a solid organ than with (non-vascularised) tissue. In Germany vascularised composite tissue is not covered by the law on transplantations [14]. A possible solution to this problem could be the French approach where composite vascularised tissue is legally equivalent to solid organs.

Meeting the costs

In all European CTA-centres the financial effort for a CTA is very high. Costs are met differently from one national system to the next: in France and Poland there is a dual financing system composed of public funding and health insurance. In Munich for the double upper arm transplantation the costs were € 150,000 plus € 50,000–70,000 annually and were covered exclusively by the health insurers. Liver transplantation at the University Hospital Heidelberg, Germany costs € 150,000–200,000.

Conclusion

CTA can be successful only at specialized designated centres due to the enormous logistical, organisational and financial challenges. A European network with a central coordination office for CTA should be established to make use of synergies, promote the professional exchange between health care providers and optimise the use of available tissue, for example, in case of a single limb transplantation to use the other limb for another patient on the waiting list. This is of great importance since an optimal match between donor and recipient not only depends on HLA-compatibility but also on phenotypic features such as skin colour, age, hair growth patterns, size, sex. The advancement of CTA as an important tool in reconstructive surgery requires deciding how costs will be met and how unsolved ethical questions should be answered.

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