Dental management of patients with organ and bone marrow transplants – preventive and therapeutic aspects

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Abstract. Solid organ and bone marrow transplant is an important therapeutic measure in end-stage diseases. The success or failure of the transplantation procedure depends on the immunity of the person involved: the graft will either be accepted or rejected. To prevent rejection, immunosuppressive drugs will be administered, which will induce several adverse reactions throughout the body, including the oral cavity. The aim of this paper is to make the dentist aware of the particularities of patients who will receive or have already received a graft: the general medical aspects, the specific medication and the necessity of a well adapted dental treatment plan.

Key-Words: organ transplant, bone marrow transplant, dental treatment

1. Introduction

Organ transplant represents a new chance to life and for the patients with severe affections, with various serious diseases like terminal renal, hepatic or cardiac failure. Nowadays, transplant operations are successfully performed in specialized clinics all over the world. Depending on the degree of compatibility between the donor and the recipient, there can also be performed heart, lungs, liver, kidney, pancreas, bone marrow, etc. Of course, the ideal combination implies the transplant of an organ from a donor who is genetically identical to the recipient – transplant between identical twins - iso/syngeneic transplant or iso/syngeneic graft. The following compatibility, with very good chances for survival, is represented by the transplant from a donor who is not genetically identical with the recipient – allograft or allogeneic transplant, the most used type of transplant. Allograft can be donated by a living-related person (parent, sibling), a living-unrelated person or a person who has died (cadaveric allograft). Transplantation of an organ from a donor to a recipient of a different species refers to xenograft or xenogeneic transplant (baboon or pig to human) [10, 11]. The most large organ base for transplant constitutes of the cadaver organs sampling (allograft), using the kidney for that type of transplant is increasing rapidly, considering the limited number of the living donors.

2. Immunosuppressive therapy

The success of the transplant depends on the immune reactivity, which may trigger the rejection or reject phenomena. The role of the immunosuppressive drugs is to inhibit the immune reactivity and they are administered, in general, after performing the transplant. The immunosuppressive agents used nowadays for the majority of the cord, liver, kidney and pancreas transplants are: cyclosporine, azathioprine, mycophenolate mofetil, prednisone, tacrolimus, anti-lymphocyte agent, etc. The best results may be obtained with the help of the triple immunosuppressive therapy – cyclosporine, prednisone and azathioprine or mycophenolate mofetil). In the case of the bone marrow transplants are used, with good results, as immunosuppressive agents, cyclosporine, prednisone and methotrexate. But the immunosuppressors agents may cause major side effects with important implications over the oral cavity. According to the Wynn and collab [14], the immunosuppressive therapy may determine the following complications in the oro-maxillo-facial sphere: gingival enlargement, gum bleeding, various forms of gingivitis, glossitis, xerostomia, halitosis, abnormal taste, esophagitis, oral ulcerations, fungal and viral infections, stomatitis, anemia, etc. The immunosuppressive therapy has also a permissive effect over the viral proliferation and namely over the development of "de novo" malignancies in the oro-maxilo-facial area, such as: epithelial dysplasia,
squamous oral carcinoma, basal cell carcinoma, Kaposi's sarcoma, etc. The incidence of "de novo" malignancies increases proportionally to the time period since the transplant, from a rate of incidence of 10% after 10 years, to 40% after 20 years after the transplant [12, 15]. For instance, azathioprine, an immunosuppressive antimetabolite, may produce hepatotoxicity and bone marrow suppression, leading to leucopenia, trombocytopenia and anemia, and in oral cavity may determine a considerable increase of the risk for infections to appear and for the occurrence of "de novo" malignancies. Taking into consideration these reactions, the cyclosporine may successfully replace azathioprine as a key drug in transplants, because it does not produce the suppression of the bone marrow. Although, cyclosporine may cause hepatotoxicity and nephrotoxicity, leading to the occurrence of hypertension, coagulation disorders and anemia, but it may increase the incidence of gingival hypertrophy/hyperplasia, hirsuitism and gynecomastitis, but also of skin cancer. Gingival hypertrophy may have prevalence and a severity proportional to the concomitant use of cyclosporine, especially cyclosporine A with drugs which have the role of reducing hypertension, like the calcium channel blockers (nifedipine, verapamil, diltiazem and others). Clinical manifestations of gum hypertrophy: it initially starts at 1-3 months since the beginning of the treatment, at the interdental papillae and then affects marginal and papillary tissues, while the tissues in edentulous areas seem not to be affected, sometimes the papillary lesions have a cauliflower appearance, of big dimensions, causing mastication, speech, esthetic disorders and changes in the position of the teeth and the occlusion. There was noticed that it especially affects male patients, and the symptoms are more severe at young patients [12]. The use of tacrolimus as a "rescue therapy" in the cases of post-transplant rejection, but also with patients with nephrotoxicity induced by cyclosporine A, represent an efficient alternative due to the absence of several major side effects such as: gingival hypertrophy/hyperplasia or arterial hypertension [16, 17]. Prednisone may determine the occurrence of hypertension, hyperglycemia, osteoporosis, psychoses, but also an increased risk for the appearance of infections and for the delay in the healing process. Usually, the immunosuppressive regime may vary a little from one medical center to another, in what concerns the doses, the moment of administration and the period of time when various immunosuppressive agents are used [3, 4, 5, 11].

3. Pre- and post-transplant medical considerations

3.1 In pre-transplant phase

In what concerns the patients who are prepared for the performance of a transplant, there must be attached a special attention to certain medical problems which may occur during the dental treatment, considering the fact that the patient is confronting the terminal phase of sickness of an organ.

That is why the preventive and therapeutic dental conduct should be established in collaboration with the surgeon and/or the team who will perform the transplant. There should be a thorough examination of the oro-maxilo-facial area, in order to early diagnosis and treat any affection appeared at this level, especially any infection or oral problem which would need a surgical intervention in the immediate phase post-transplant, when the transplant is very sensitive to infections.

Also, it is preferable to avoid any post-transplant dental treatment, for a variable period of time (usually approx. 6 months), due to certain manifestations such as: fatigue, drugs interaction and side effects of the drugs administered during the post-transplant treatment. There should be taken into account the fact that the patient who will suffer a bone marrow transplant is in general prone to infection, bleeding and delayed healing, due to the leucopenia and trombocytopenia. Furthermore, the patients who will suffer a hepatic transplant present the risk of massive bleeding during the dental treatment, due to the coagulopathy, and patients who will suffer a renal transplant and periodically have hemodialysis, may need preventive antibiotherapy before the dental treatment, in order to prevent the occurrence of bacterial endocarditis, but also the monitorization of the blood pressure, due to the arterial hypertension, as sign of renal disease.

Thus, the dentist shall take into account the fact that, in what concerns certain drugs used before or during the dental treatment and metabolized at a renal and hepatic level, he should modify the doses or even avoid their use. Ibuprofen, as non-steroidal anti-inflammatory, may be used in renal failure, while in the hepatic failure its effects are not known. The administration of antibiotics such as: Tetracycline (Doxycycline) and Cefalexine (Keflex) should be usually avoided or the time period between the doses should be increased [10, 11]. In what concerns certain anesthetics, such as Lidocaine/ Xilocaine, Aronoff and collab assert in one study [18] that this may be usually used, but
only if the time period between the doses is increased, or if it’s possible, it should be avoided, while Byrne [19] states that it may be used without the change of the doses, both in end-stage renal and hepatic disease. The preventive dental conduct shall focus on providing an optimal oral health to the patient before the surgical intervention, also taking into consideration the dental history, the ability of the patient to make in good conditions the hygienization of the oral cavity in the posttransplant phase and the general medical stability of the patient. The general medical state of the patient and the success of the transplant constitute priorities in making a dental treatment plan in the case of a patient who will have a transplant [10, 11].

3.2 In posttransplant phase

For a better management of a patient with organ transplant, the dentist should be aware of the medical aspects characteristic for the stages of the posttransplant period: the immediate posttransplant period, the stable posttransplant period and the chronic rejection period [1, 2, 6, 11]. Although the immunosuppressive agents such as: cyclosporine, prednisone and azathioprine have an important contribution to preventing the rejection and to the increase of the survival rate, they still have major side effects which increase the risk of the occurrence of bacterial infections (with Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola), viral infections (with herpes simple virus, cytomegalovirus, Epstein-Barr virus) or fungal infections (C. albicans, C. dubliniensis and C. hyphae) [12].

Also, there are drugs used by the dentists such as erythromycin, metronidazole, tetracyclines, phenytoin, and others [8, 10], which may interact with the cyclosporine and others immunosuppressive agents.

For all these reasons, to the patient it will be performed only the emergency dental treatment and only in collaboration with the patient’s attending physician, who may decide the pertinence of the use of antibiotic prophylaxis in view of preventing the bacterial endocarditis, according to a specific treatment regimen based on the norms of the American Heart Association (Table 1) [10, 13]:

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Oral medications</th>
<th>Non-oral medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults not allergic to penicillin</td>
<td>procedure</td>
<td>before procedure</td>
</tr>
<tr>
<td>Adults - penicillin allergic</td>
<td>Cephalexin – 2 g, 1 h before procedure or Clindamycin – 600 mg, 1 h before procedure (there are some studies which specify that Clindamycin should not be used in most organ transplant patients because of acute liver toxicity [10])</td>
<td>Cefazolin – 1 g IM or IV, 30 min before procedure or Clindamycin – 600 mg IV, 30 min before procedure</td>
</tr>
</tbody>
</table>

Table 1 – Standard regimens for antibiotic prophylaxis to prevent bacterial endocarditis during dental treatment

On the basis of the AHA norms, Dajani and collab [20] have outlined the oral procedures which requires prophylactic antibiotic therapy (Table 2):

<table>
<thead>
<tr>
<th>Oral procedures that requires prophylactic antibiotic therapy</th>
<th>Oral procedures that, usually, do not requires prophylactic antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental extractions</td>
<td>Prosthetic procedures with/without retraction cord, including the restoration of the teeth affected by dental caries</td>
</tr>
<tr>
<td>Periodontal procedures including the surgical ones, scaling and root planning</td>
<td>Insertion of certain removable prosthetic or orthodontic appliances</td>
</tr>
<tr>
<td>Dental implants placement and teeth re-implantation.</td>
<td>Impression taking</td>
</tr>
<tr>
<td>Endodontic instrumentation (beyond the apex) or surgery</td>
<td>Endodontic procedures, including post placement and buildup</td>
</tr>
<tr>
<td>Intraligamentary injections</td>
<td>Local anesthetic injections (non-intraligamentary)</td>
</tr>
<tr>
<td>Prophylactic cleaning of teeth, where bleeding is anticipated</td>
<td>Local fluoridation</td>
</tr>
<tr>
<td>Other procedures in which major bleeding is anticipated</td>
<td>Exfoliation of primary teeth</td>
</tr>
</tbody>
</table>

Table 2 – Oral procedures that requires prophylactic anti-biotherapy
The following posttransplant stage is the one when the graft is stable and functional, namely at 3 months after the transplant. During this period, the main concern constitutes of the over-immunosuppression, which increases the risk for the infections or infra-immunosuppression to occur, which increases the risk for the graft acute rejection occurrence. The period of the chronic rejection starts slowly, insidious, by associated signs and symptoms, usually with organ failure and it’s irreversible. This may lead to the necessity of retransplantation or even to death, in the case of the cardiac or hepatic transplants, while the renal transplants may need dialysis or even retransplantation [1, 2, 6].

4. Dental management – prophylactic and therapeutic conduct

4.1 In pretransplant phase

In a first phase, the patients who are being prepared for an organ transplant should go under an attentive un-invasive oral examination, after previously studying the medical and dental history. In case of patients with a good oral hygiene, a special emphasis shall be laid on oral health education, referring to the instruction, motivation of the patient and the control of his capacity to comprehend, to digest and fulfill in an efficient way the techniques of removing the microbial dental plaque. The oral health education shall be supplemented by the education for a correct and balanced alimentation [9]. Before the transplantation, all the active dental caries should be treated and non-vital teeth should be endodontically treated or extracted at these patients. In case of patients with a poor oral hygiene and who are not motivated to improve their oral health level, there should be taken into account the extraction of teeth that cannot be treated due to the evolution of the dental caries and of teeth affected by advanced periodontal disease and there will be performed dentures [1, 2, 3, 6].

Dental management of the patient before an organ transplantation may be summarized as follows [7, 10, 12]:

a. Initial consultation of the patient’s attending physician, in order to discuss the current medical state of the patient and of the laboratory blood tests, but also for the opportunity to introduce the antibiotic prophylaxis or certain drugs, as well as their doses;

b. Conduct a complete series of radiographs for the dentate patients and a panoramic dental x-ray for the edentulous patients [21];

c. Attentive oro-maxilo-facial examination, considering the potential development of "de novo" malignancies at this level;

d. Remove of the microbial dental plaque by plaque control techniques and a careful instruction in view of the oral self-hygienization, both by the individualization of the dental brushing technique, but also by using certain means additional to dental brushing. There will be taken into consideration the use of electric toothbrushes and oral irrigators. The parents of the pediatric patients will be instructed to perform/supervise their child oral hygiene;

e. Prescribe fluoridated toothpastes and perform topical fluoridation with custom fluoride trays, in case of multiple dental caries;

f. Instruct in view of changing the diet, if necessary;

g. Perform mechanical debridement and root planning, taking into consideration the introduction of the antibiotic prophylaxis;

h. Use chlorhexidine 0.12% mouthwash, which may be beneficial as antimicrobial and anti-fungal, by rinsing before any dental procedures;

i. Try to maintain the teeth by endodontic treatment (preferred over extraction);

j. Perform extraction of the nonrestorable teeth, using suturing techniques and haemostatic agents in order to ensure the haemostasis;

k. Use pain management with Acetaminophen (Paracetamol, Tylenol) in adjusted doses. The administration of Aspirin shall be avoided, because it increases the bleeding potential.

4.2 In posttransplant phase

Considering the increased potential of the post-surgery complications and of the hyperacute or acute graft rejection, during the immediate posttransplant period (the first 3 months) there shall be NO routine dental treatment. The only dental treatment allowed is the noninvasive emergency procedures, but only after taking counsel together with the attending surgeon. During the stable posttransplant period, usually between 3-6 months after the surgery, when the graft is in healing process and the reactions of acute rejection are under attentive control, the patient is considered to be in a stable phase, allowing to continue the election dental treatment.

Dental management of the stable patient in posttransplant phase may be synthesized as follows [1, 2, 7, 8, 10, 12, 22]:

a. Daily control of the microbial dental plaque,
on basis of an oral hygiene program established since pretransplant phase, using extra soft toothbrushes for sensitive teeth, mild toothpaste without whitening or tartar control agents to avoid irritation of a dry mouth, mouthwashes containing chlorhexidine 0.12% or without alcohol;

b. Attentive examination for an early discovery of dental infection, since immunosuppressive medication can hide signs of such a problem. Thus, the infections may be often in an advanced phase when detected and should be treated accordingly;

c. Check patient's blood pressure before the beginning of the dental treatment and if it exceeds accepted levels call immediately patient physician;

d. Management of patient's excessive bleeding potential, using blood screening tests and establishing special precautions, depending on the particularities of the case;

e. Conduct quadrant scaling and of root planning in gingival inflammations, with the eventuality of introducing antibiotic prophylaxis. Use caution when prescribing an antibiotic due to potential nephro- and hepatotoxicity;

f. Avoid certain drugs that are toxic to liver or kidney – non-steroidal anti-inflammatory drugs, local (amides) or general anesthetics (halothane), sedatives (barbiturates, long-acting benzodiazepines), etc;

g. At patients with xerostomia use synthetic saliva substitutes, sugar-free chewing gum to stimulate salivary flow and prescribe 1,1% neutral sodium fluoride toothpastes, 0.63% stannous fluoride rinse or 0.4% stannous fluoride gels to minimize the potential of occurrence of root caries [14];

h. At patients with oral candidiasis use local antifungal medications: clotrimazole troche 10mg (1 troche slowly dissolved in the oral cavity, 5 times/day, 14 consecutive days) and nystatin oral suspension 5 ml (1 teaspoon maintained in the oral cavity for 2 minutes and then swallowed) [14];

i. Counsel the patient for a meticulous oral self-hygienezation and emphasize the importance of maintaining a good oral health, both before and after the transplantation;

j. Initiate an active recall program every 3-6 months, depending on the particularities of the case.

5. Conclusions

5.1 Organ and bone marrow transplant addresses to the marked patients, with end-stage diseases such as: cardiac, hepatic or renal failure, aplastic anemia, chronic myelogenous leukemia, thalassaemia, falciform anemia or major genetic immunodeficiency.

5.2 The success of an organ or bone marrow transplant depends on the immune reactivity of the recipient organism, which may trigger the rejection phenomena. The immunosuppressive drugs, administrated in the posttransplant phase have the role of inhibiting the immune reactivity, but they have also side effects, with implications at the level of oral cavity, which should be known also by the dentist.

5.3 Both in the pretransplant and posttransplant phase, the dentist should take into account the general medical state of the patient which shall go under any dental treatment. The general medical state of patient and the success of transplantation are priorities in drafting a dental treatment plan, in the case of any patient which shall have a transplant.

5.4 The efficient dental treatment may have an important role in the favorable posttransplant evolution, especially by preventing the occurrence of severe infections.

5.5 For an optimal dental management of the patients who are in either, pre- or posttransplant phase, it is necessary a permanent collaboration with patient’s attending physician.

References:


