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Orale Mukositis bei stammzelltransplantierten Patienten: Epidemiologie, Prävention, Therapie und Lebensqualität im klinischen Alltag.

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Abkürzungsverzeichnis

CTCAE .....Common Terminology Criteria for Adverse Events
HLA ..... Human leukocyte antigens
NCI ..... National Cancer Institute
NRS..... Numerische Rating Skala
OM .....Orale Mukositis
OMDQ .....Oral Mucositis Daily Questionnaire
OTS.....Oral Toxicity Scale
WHO ..... World Health Organisation

I. Einleitung

Neben der eigentlichen Behandlung von soliden Tumoren, Leukämien, Lymphomen und Metastasen ist in der Onkologie auch die Behandlung von therapieinduzierten Erkrankungen von höchster Bedeutung. Eine dieser Begleiterkrankungen ist die orale Mukositis (OM), die als Nebenwirkung von Chemotherapeutika und/oder Radiotherapien auftritt [Epstein 1999]. Besonders im Rahmen von Stammzelltransplantationen, bei denen in den meisten Fällen aggressive Chemotherapeutika - oft in Kombination mit Ganzkörperbestrahlungen - notwendig sind, ist die orale Mukositis eine häufige Nebenwirkung [Vagliano 2011].

I.1. Stammzelltransplantation

I.1.1. Definition und Einteilung

Der Begriff Stammzelltransplantation beschreibt die Übertragung von blutbildenden Stammzellen - Körperzellen, die in der Lage sind, sich in verschiedene der im Blut vorhandenen Zelltypen auszudifferenzieren - von einem Spender auf einen Empfänger [Hatzimichael 2010].

Stammzelltransplantationen ermöglichen die Verwendung von höheren Dosen an Radio-/Chemotherapien, die ohne Transplantation tödlich wären. Nach Verabreichung eben dieser Myeloablation werden dem Patienten gesunde Stammzellen transplantiert, um die normale Funktion des Knochenmarks wiederherzustellen und einer lebensbedrohlichen Panzytopenie vorzubeugen [Hatzimichael 2010, Juric 2016].

Man unterscheidet Stammzelltransplantationen grundsätzlich in autologe und allogene Stammzelltransplantationen. Bei autologen Stammzelltransplantationen sind Spender und Empfänger der Stammzellen identisch. Im Rahmen von autologen Stammzelltransplantationen werden dem Patienten vor einer Chemo- und/oder Radiotherapie Stammzellen entnommen und nach Therapieende transplantiert. Die häufigsten Erkrankungen, die eine autologe Stammzelltransplantation erfordern, sind Plasmozytome und Lymphome, da ihre

Therapie aggressive Chemo- und Radiotherapieregime erfordert [Gyurkocza 2010, Hatzimichael 2010].

Bei allogenen Stammzelltransplantationen erhält der Patient Stammzellen eines gesunden Spenders. Der Spender wird im Vorfeld über übereinstimmende Gewebemerkmale (human leukocyte antigens (HLA)) identifiziert. Meist werden allogene Stammzelltransplantationen benötigt, wenn das Knochenmark selbst von der Grunderkrankung betroffen ist und somit keine Möglichkeit einer autologen Stammzelltransplantation besteht. Häufige Erkrankungen, die eine allogene Stammzelltransplantation erfordern, sind akute und chronische Leukämien sowie myelodysplastische und myeloproliferative Syndrome. Hier werden die Stammzellen ebenfalls nach einem Chemo-/Radiotherapieregime transfundiert, mit der im besten Fall die Grunderkrankung beseitigt oder vermindert wurde [Gyurkocza 2010, Hatzimichael 2010, Juric 2016].

I.1.2. Komplikationen

Im Rahmen der Stammzelltransplantation können verschiedene Komplikationen auftreten. Chemo- und Radiotherapien schädigen vor allem die sich schnell und ständig teilenden Zellen. Dies betrifft zwar vor allem das eigentliche Ziel - das Tumorgewebe - jedoch werden auch andere sich schnell teilende Gewebearten wie die Haarwurzelzellen, Blutstammzellen, Gonaden oder Schleimhautzellen geschädigt. Somit kann es zu Haarausfall, Anämien und/oder Entzündungen der Schleimhäute - der sogenannten Mukositis – kommen [Juric 2016, Miller 2012].

Häufig kommt es zudem durch die Chemotherapien akut zu Übelkeit, Hautausschlägen, Erbrechen und Durchfall. Chronisch können je nach eingesetzter Substanz Organschäden zum Beispiel in Lunge, Leber, Niere und Nervensystem auftreten. Nach der Konditionierungsphase kann es durch das durch die Chemo-/Radiotherapie supprimierte Immunsystem zu schweren opportunistischen Infektionen (z. B. invasive Aspergilllose) oder zur Reaktivierung von latenten Infektionen (z. B. Cytomegalievirus) kommen. Zudem besteht das Risiko eines Transplantatversagens oder – speziell bei allogenen Stammzelltransplantationen - einer Abstoßungsreaktion [Gyurkocza 2010, Hatzimichael 2010, Juric 2016].

Bei allogenen Stammzelltransplantationen besteht das zusätzliche Risiko einer Graft-versus-Host-Disease. Trotz HLA-identischen oder HLA-ähnlichen Stammzellen reagieren die transplantierten Immunzellen gegen den Wirtsorganismus. Im Rahmen dieser Abwehrreaktion kann es zu Schäden der Haut, Leber, des Magen-Darm-Trakts und des hämatopoetischen Systems kommen, die als Ausschläge, Bauchkrämpfe, veränderte Leberwerte und/oder Diarrhoe klinisch sichtbar werden. Weiterhin kann es nach der Transplantation zu einem Rezidiv der Grunderkrankung oder durch die Immunsuppressiva zu weiteren sekundären Neoplasien kommen [Hatzimichael 2010, Tabbara 2002].

I.2. Orale Mukositis

I.2.1. Definition

Die orale Mukositis beschreibt einen entzündlichen, oft auch ulzerierenden Prozess der Mundschleimhaut. Sie tritt häufig im Verlauf einer Chemo- oder Radiotherapie auf und ist assoziiert mit Schmerzen, Schluck- und Sprechstörungen, Rötungen, Ödemen und pseudomembranösen Belägen der Mundschleimhaut [Blijlevens 2000, Scully 2006]. Die Entwicklung einer Mukositis beschränkt sich nicht nur auf die Mundschleimhaut, sondern betrifft auch die Schleimhäute des gesamten Magen-Darm-Trakts; der Begriff orale Mukositis bezieht sich nur auf den oropharyngealen Teil dieser Veränderungen [Blijlevens 2000].

I.2.2. Einteilung

Die orale Mukositis besitzt kein einheitliches Graduierungssystem - es werden sowohl in der Literatur als auch in der Praxis verschiedenste Skalen verwendet. Die zwei am häufigsten verwendeten Skalen sind die „Oral Toxicity Scale“ der World Health Organisation (WHO-OTS) und die „Common Terminology Criteria for Adverse Events“ des National Cancer Institutes der Vereinigten Staaten (NCI-CTCAE). Die Einteilung erfolgt anhand symptomatischer (zum Beispiel Schmerzen), anatomischer (zum Beispiel Ulzerationen) und funktioneller Kriterien (zum Beispiel ob die Nahrungsaufnahme möglich ist). Neben diesen von Ärzten und Pflegepersonal verwendeten Instrumenten gibt es zusätzlich

noch Patientenfragebögen, wie z. B. der OM Daily Questionnaire (OMDQ). [Bonomi 2015, National Cancer Institute June 14, 2010, World Health Organization 1979].

Tabelle 1: Einteilung der Schweregrade der oralen Mukositis

Grad	WHO-OTS[1]	NCI-CTCAE[2]
0	Keine Veränderungen	-
1	Rötung, Schmerzen	Asymptomatisch oder milde Symptome, keine Intervention indiziert
2	Rötungen, Ulzerationen, kann feste Nahrung zu sich nehmen	Mäßige Schmerzen oder Ulzerationen, interferiert nicht mit oraler Nahrungsaufnahme, modifizierte Diät ist indiziert
3	Ulzerationen, benötigt flüssige Ernährung	Schwerer Schmerz, interferiert mit der oralen Nahrungsaufnahme
4	Orale Nahrungsaufnahme nicht möglich	Lebensbedrohliche Konsequenzen, dringende Intervention nötig
5	-	Tod

[1] [World Health Organization 1979]; [2] [National Cancer Institute June 14, 2010]

I.2.3. Pathophysiologie

Durch Chemo- oder Radiotherapien kommt es zu Schäden in der DNA und anderen Zellbestandteilen der Mucosa und Submucosa. Dadurch werden Transkriptionsfaktoren, die unter anderem proinflammatorische Cytokine kodieren, hochreguliert und Enzyme aktiviert. Dies führt zur Apoptose von Endothelzellen und Fibroblasten in der Submucosa, die ebenfalls eine weitere Ausschüttung von Mediatoren und weitere Gewebszerstörungen nach sich ziehen. Je nach Intensität und Dauer dieser Schleimhautreaktion können Verletzungen in der Schleimhaut auch klinisch nachgewiesen werden. Diese Ulzerationen sind durch bakterienhaltige fibrinöse Beläge begleitet, die weiterhin zur Aktivierung von Makrophagen und einer damit verbundenen Entzündungsreaktion führen. Mit dem Anstieg der weißen Blutzellen nach der Stammzelltransplantation beginnt die Migration, Proliferation und Differenzierung von Epithelzellen, wodurch die Ulzerationen wieder verschlossen werden [D'Hondt 2006, Sonis 2004].

I.2.4. Epidemiologie

Die Inzidenz der oralen Mukositis und die Verteilung ihrer Schweregrade ist abhängig von dem Therapieschema der Chemo- und/oder Radiotherapie, den persönlichen Risikofaktoren und den prophylaktischen Maßnahmen [Barasch 2003]. Auf die Angaben zu Inzidenz und Schweregrade der oralen Mukositis in der Literatur nehmen noch zusätzlich die Instrumente (wie z. B. WHO-OTS), die in der jeweiligen Studie zur Erfassung der oralen Mukositis verwendet wurde, Einfluss. Durch die Erfassung von unterschiedlichen klinischen Aspekten der oralen Mukositis durch die Instrumente kann es hierbei zu Differenzen in der Graduierung zwischen zwei Instrumenten kommen. Zudem werden meist von Patienten selbst berichtete Symptome, wie z. B. im OMDQ-Fragebogen, als schlimmer empfunden [Bonomi 2015].

Als therapieunabhängige Risikofaktoren für die Entwicklung einer oralen Mukositis wurden das weibliche Geschlecht, höheres Alter, bereits vorher aufgetretene orale Mukositis sowie ein erhöhter oder erniedrigter Ernährungszustand identifiziert [Elting 2003, Raber-Durlacher 2000, Robien 2004, Zalcberg 1998]. Patient mit einer positiven Rauchanamnese und vorherige Chemo- oder Radiotherapie litten weniger unter einer oralen Mukositis [Patussi 2014, Raber-Durlacher 2000]. Therapieabhängig wurde das Auftreten einer oralen Mukositis verstärkt beim Einsatz von Ganzkörperbestrahlung sowie beim unverwandten Stammzellspendern gefunden [Barasch 2003, Robien 2004, Vera-Llonch 2007].

Zwischen 26 % und 77 % der Patienten mit soliden Tumoren entwickeln im Rahmen ihrer Chemotherapie eine orale Mukositis [Nishimura 2012, Tachi 2015]. Bei Patienten mit Kopf-Hals-Karzinomen mit kombinierter Radiochemotherapie erkrankten zwischen 88 % und 100 % an einer oralen Mukositis [Hu 2014, Vatca 2014]. Bei Hochdosischemotherapien, die vor allogenen und autologen Stammzelltransplantationen durchgeführt werden, erkranken je nach Therapieschema und Dosis, zwischen 40 % und 96 % der transplantierten Patienten [Jones 2008, Urbain 2012].

Schwere orale Mukositis (Grad III und IV OM) tritt bei Hochdosischemotherapien mit einer Wahrscheinlichkeit zwischen 20 % und 67 % auf [Urbain 2012, Wardley

2000]. Bei stammzelltransplantierten Patienten, die eine Hochdosischemotherapie mit oder ohne Ganzkörperbestrahlung erhalten haben, beginnt die orale Mukositis im Median am 5. Tag nach der Stammzelltransplantation. Am 15. Tag nach der Stammzelltransplantation sind über 90 % der Patienten wieder frei von Schleimhautveränderungen [Woo 1993].

I.2.5. Symptome

Durch die Schleimhautveränderungen im Rahmen der oralen Mukositis leiden die Patienten unter schmerzhaften Rötungen bis hin zu Ulzerationen im gesamten Oropharynx [Blijlevens 2000]. Patienten mit Entwicklung einer oralen Mukositis leiden deutlich häufiger an starken Schmerzen, als Patienten ohne Entwicklung einer oralen Mukositis. Je nach Intensität der Schmerzen sind die betroffenen Patienten auf opioide Analgetika angewiesen, die wiederum zusätzliche Nebenwirkungen mit sich bringen [Bellm 2000].

Die orale Mukositis schränkt die Patienten je nach Ausmaß der Symptome in ihrer Fähigkeit zu essen, schlucken, trinken und sprechen ein. Durch Schmerzen und Geschmacksveränderungen sind die Patienten vor allem in der oralen Nahrungsaufnahme eingeschränkt [Bellm 2000]. Die reduzierter Speichelproduktion und verstärkte Schleimproduktion wirken sich überwiegend auf die Kommunikationsfähigkeit der Patienten aus [Blijlevens 2000]. Patienten mit oraler Mukositis leiden häufiger unter körperlichen Schwächezuständen als Patienten ohne orale Mukositis [Elting 2003]. Diese Symptome schränken den Patienten vor allem in seiner Alltagskompentenz ein und haben somit auch großen Einfluss auf die Lebensqualität [Bellm 2000].

I.2.6. Komplikationen

Es wird angenommen, dass der Barrieredefekt der Mundschleimhaut, der durch eine orale Mukositis hervorgerufen wird, das Entstehen von Infektionen begünstigt [Elting 2003]. Mit dem Auftreten einer oralen Mukositis steigt auch das Risiko, an lebensbedrohlichen Bakteriämien und Fungämien zu erkranken [Bergmann 1989, Ruescher 1998].

Der Zusammenhang zwischen der oralen Mukositis und dem Auftreten von Blutungen ist noch nicht vollständig geklärt. Während Elting et al. lediglich Zusammenhänge zwischen dem Auftreten von gastrointestinaler Mukositis und Blutungen gefunden haben, fanden Kim et al. eine Häufung von oralen Blutungen bei Patienten mit soliden Tumoren und oraler Mukositis [Elting 2003, Kim 2012].

Durch den Funktionsverlust beim Essen, der durch die orale Mukositis hervorgerufen wird, ist das Auftreten einer oralen Mukositis mit einem signifikanten Gewichtsverlust assoziiert [Elting 2007]. Dadurch sind die Patienten auf eine parenterale Nahrungszufuhr angewiesen [Sonis 2001].

All diese Komplikationen - allein oder in Kombination - können zu einem verlängerten Krankenhausaufenthalt oder Veränderungen im Therapieschema der Patienten führen [Lalla 2008, Sonis 2001].

I.2.7. Prävention und Therapie

Die Deutsche Krebsgesellschaft, die Deutsche Krebshilfe und die Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF) haben im April 2017 die zum Stand dieser Arbeit aktuellsten Empfehlungen zur Prävention und Therapie der oralen Mukositis bei stammzelltransplantierten Patienten herausgegeben [Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft 2017].

Zur Prävention empfehlen diese Leitlinien Mundspülungen mit Wasser oder 0,9 % Kochsalzlösung, Pflege der Zähne mit weicher Zahnbürste, Reinigung der Zahnzwischenräume, Vermeidung von Noxen, Fortlaufende Kontrollen auf Läsionen und Schmerzen, Risikoadaptierte vorbeugende Maßnahmen durch den Zahnarzt und eine engmaschige klinische Kontrolle. Außerdem wird zur Durchführung von oraler Kryotherapie bei Hochdosis-Melphalan-Chemotherapien geraten. Für die Verwendung von Low-Level-Lasertherapie und rekombinantem humanem Keratinozytenwachstumsfaktor-1 (Palifermin) kann keine Empfehlung ausgesprochen werden. Sucralfat, intravenöses Glutamin, Granulozyten-Makophagen-Kolonie-stimulierender Faktor, Pentoxifyllin und

Pilocarpin sollen nicht zur Prophylaxe der OM angewendet werden [Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft 2017].

Zur Therapie der oralen Mukositis sollen orale Mundpflegeprotokolle angewendet werden, bei Bedarf sollen intravenöse Opioide und Doxepin-Mundspülungen zur Schmerztherapie angewendet werden. Für die Therapie der oralen Mukositis mit Low-Level-Lasertherapie wird keine Empfehlung ausgesprochen. Sucralfat sollte nicht für die Therapie der oralen Mukositis verwendet werden [Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft 2017].

I.3. Zielsetzung und Kausale

In Deutschland gibt es kaum Zahlen zur Epidemiologie der oralen Mukositis und dem Auftreten von Komplikationen. Zudem fehlen Erhebungen über die Prävention und Therapie der oralen Mukositis und den damit verbundenen Kosten im klinischen Alltag. Aktuelle Untersuchungen zum Einfluss der oralen Mukositis auf die Lebensqualität der Patienten in Deutschland gibt es fast nicht. Vor diesem Hintergrund war es Ziel der hier vorliegenden Arbeit, die Inzidenz der oralen Mukositis in der medizinischen Klinik und Poliklinik III des Klinikums der Universität München der Ludwig-Maximilians-Universität darzustellen. Weiterhin sollte die Häufigkeit von Komplikationen und die Stärke der Symptome, die im Zusammenhang der oralen Mukositis stehen bestimmt werden und der Einfluss der oralen Mukositis auf die Lebensqualität der Patienten ermittelt werden. Die Therapie- und Präventionsmaßnahmen sollten im klinischen Alltag erfasst werden und dadurch der Ressourcenverbrauch und die damit verbundenen Kosten bestimmt werden.

I.4. Zusammenfassung der vorliegenden Arbeiten

Im Vorfeld von klinischen Therapiestudien ist es sinnvoll, die aktuelle Versorgung der Patienten darzustellen, um zum einen die Ausgangslage richtig einschätzen zu können und zum anderen bereits existierende mögliche Schwachpunkte in der Versorgung zu identifizieren. Beide hier vorgestellten Arbeiten sind Teil einer Pilot-Studie zur Darstellung der aktuellen Versorgung der oralen Mukositis im klinischen Alltag in Deutschland. Dazu wurden in einem Zeitraum von 7 Monaten

alle stammzelltransplantierten Patienten der medizinischen Klinik und Poliklinik III des Klinikums der Universität München, die die für diese Studie benötigten Kriterien erfüllten, beobachtet. Die Patienten wurden nach einem Basisassessment vor der Stammzelltransplantation ab dem Zeitpunkt der Stammzelltransplantation drei Mal wöchentlich besucht und auf das Auftreten einer oralen Mukositis untersucht und zu weiteren Symptomen befragt. Für die Erfassung aller studienrelevanter Daten wurde im Vorfeld ein eigener Fragebogen entwickelt. Um die Auswirkungen der oralen Mukositis festzustellen, wurden anschließend exploratorische Tests durchgeführt.

Der erste Teil der hier vorliegenden Arbeit beschäftigt sich mit dem Einfluss der oralen Mukositis auf die Lebensqualität der Patienten. Dieser Einfluss lässt sich sowohl durch eine reine Bestimmung von Scores für eine gesundheitsbezogene Lebensqualität bestimmen, als auch durch lebenqualitätsbezogene Symptomskalen (zum Beispiel Schmerz) und lebenqualitätsbezogene Funktionsskalen (zum Beispiel körperlicher Funktionszustand). Hierzu wurde als validiertes und zuverlässiges Instrument der EORTC QLQ-C30 und EORTC QLQ-OH15 verwendet [Hjermstad 2016, Shih 2013]. Patienten mit oraler Mukositis litten häufiger unter Schmerzen und einem wunden und sensiblen Mund. Trotz adäquater Schmerztherapie, gab knapp ein Fünftel (19 %) der von der oralen Mukositis betroffenen Patienten an, unter schweren Schmerzen zu leiden. Dies entspricht einer Punktzahl von 7-10 Punkten auf der numerischen Rating-Skala (NRS). 35 % der Patienten gaben an, dass sie mäßige Schmerzen ertragen (NRS 4-6). Es wurde eine positive Korrelation zwischen Grad der oralen Mukositis und Intensität des Schmerzes auf der numerischen Rating-Skala gefunden ($r=0.80$, 95 % CI: 0.76-0.84, $p<0.001$). Zudem konnte eine negative Korrelation zwischen dem mittlen Schmerzwert auf der NRS während der ersten Woche und der Lebensqualität der Patienten ($r=0.74$, 0.55-0.85, $p<0.001$) gefunden werden. Sieben Tage nach der Stammzelltransplantation konnte ein Abfall der körperlichen Funktionsfähigkeit (34.5 vs. 7.5, $p=0.003$) bei Patienten mit Entwicklung einer oralen Mukositis gefunden werden. Zusätzlich konnte zum selben Zeitpunkt eine niedrigere Lebensqualität (24.3 vs 7.7, $p=0.006$) bei Patienten mit Entwicklung einer oralen Mukositis gemessen werden. Zusammenfassend konnte gezeigt werden, dass die orale Mukositis einen negativen Einfluss auf die Lebensqualität sowie lebensqualitätsbezogene

Symptome und Funktionen stammzelltransplantierter Patienten hat. Vor allem die durch die orale Mukositis ausgelösten Schmerzen senken die Lebensqualität der Patienten. Um die Lebensqualität der Patienten während der Stammzelltransplantation zu erhalten, muss mehr Aufmerksamkeit auf die Prävention und Therapie der oralen Mukositis gelegt werden.

Der zweite Teil der hier vorliegenden Arbeit beschäftigt sich mit der Epidemiologie der oralen Mukositis, ihrer Prävention und Therapie und den damit verbundenen Kosten. Es wurde festgestellt, dass mehr als die Hälfte (58 %) der stammzelltransplantierten Patienten während ihres Aufenthalts unter einer oralen Mukositis litt; fast die Hälfte (47 %) der von einer oralen Mukositis betroffenen Patienten litt unter einer schweren oralen Mukositis (Grad III, IV). Nach allogener Stammzelltransplantation litten die meisten Patienten zwischen dem 4. und 6. Tag und dem 14. und 15. Tag unter einer oralen Mukositis; bei den autologen Patienten häufte sich das Auftreten einer oralen Mukositis zwischen dem 7. und 10. Tag. Als Risikofaktoren für die Entwicklung einer oralen Mukositis wurden ein Alter ≥ 65 Jahre (69 % vs. 31 %, OR=3.78, CI 1.0 – 14.26, p=0.021), das weibliche Geschlecht (80 % vs. 47 %, OR=4.57, CI 1.01 – 19.67, p=0.035) und Ganzkörperbestrahlungen (77 % vs. 46 %, OR=3.75, CI 0.98 – 14.39, p=0.050) identifiziert; höhere Grade wurden bei Patienten mit unverwandten Spendern (2.63 vs. 1.29, p=0.014) und Patienten mit negativer Raucheranamnese (2.69 vs. 1.77, p=0.036) gefunden. Patienten, die unter einer oralen Mukositis litten, benötigten häufiger eine Schmerztherapie (80 % vs. 32 %, p=0.001), intravenöse Opiate (24 % vs. 0 %, p=0.023) und flüssige Ernährung (51 % vs. 11 %, p=0.004). Autolog stammzelltransplantierte Patienten mit oraler Mukositis hatten um 824 € erhöhte Gesamttherapiekosten (Ernährung, Analgesie, Anti-Infektiva) im Vergleich zu Patienten ohne orale Mukositis (p=0.037). Bei allogen stammzelltransplantierten Patienten mit oraler Mukositis wurden höhere Kosten in der Schmerztherapie gefunden (10 € vs. 2 €, p=0.034). Weniger als die Hälfte der Patienten (49%) hielt sich während des Aufenthalts an die vorgeschriebene Anzahl der Mundspülungen. Patienten ohne Entwicklung einer oralen Mukositis hielten sich häufiger an das vorgeschriebene Mundpflegeprotokoll (68 % vs. 35 %, p=0.027). 65 % der Patienten mit mangelnder oder fehlender Adhärenz konnten keinen Grund für ihre mangelnde oder fehlende Adhärenz angeben. Wir konnten zeigen, dass die orale Mukositis ein sehr häufiger Nebeneffekt bei

stammzelltransplantierten Patienten ist. Die Adhärenz der Patienten hinsichtlich Mundspülungen ist verbesserungswürdig. Auf Patienten mit ungünstigen Risikokonstellationen sollte besonders Acht gegeben werden, um der Entwicklung der oralen Mukositis vorzubeugen und damit Ressourcen und Kosten zu sparen.

I.5. Summary of the presented publications

In advance of clinical therapy studies, it is reasonable to illustrate the current patient care in order to properly evaluate the baseline properly and in order to identify possible blind spots. Both hereby presented works are part of a pilot-study to demonstrate the current routine hospital care of Oral Mucositis in Germany. Therefore, in a time period of seven months all stem cell transplant patients of the Department of Medicine III (University Hospital – Ludwig Maximilian University of Munich) who met the required criteria for the study were observed. After a basis assessment prior to stem cell transplantation, beginning at the day of stem cell transplantation, the patients were visited three times a week and were examined for the occurrence of an Oral Mucositis and were asked about further symptoms. In order to assess the relevant data for the study a questionnaire was developed. To determine the effects of Oral Mucositis exploratory tests were conducted.

The first part of the hereby presented work deals with the influence of Oral Mucositis on the quality of life of the affected patients. On the one hand, this influence can be determined by the acquisition of scores for the health-related quality of life on the other hand it can be determined with quality of life related symptom scales (e.g. pain) and quality of life related function scales (e.g. physical functioning). Therefore, we used the validated and reliable tools EORTC QLQ-C30 and EORTC QLQ-OH15 [Hjermstad 2016, Shih 2013]. Patients with Oral Mucositis suffered more often from pain and a sore and sensible mouth. Despite appropriate pain treatment, nearly one fifth (19%) of the patients affected with Oral Mucositis indicated suffering from severe pain. This equals a score of 7 to 10 points on the Numeric Rating Scale (NRS). 35% of the patients stated that they were having moderate pain (NRS 4-6). A positive correlation between grade of Oral Mucositis and the intensity of pain on the Numeric Rating Scale (r=0.80,

95% CI: 0.76-0.84, p<0.001) was found. Additionally, a negative correlation between the mean pain value on the Numeric Rating Scale during the first week and the quality of life of the patients was found (r=0.74, 0.55-0.85, p<0.001). Seven days after stem cell transplantation a decrease of the physical function (34.5 vs. 7.5, p=0.003) in patients affected by Oral Mucositis was detected. Moreover, at the same date a lower quality of life (24.3 vs 7.7, p=0.006) was measured in patients with Oral Mucositis. In summary we could indicate the negative influence of Oral Mucositis on quality of life as well as on symptoms and functions related to quality of life in stem cell transplant patients. Especially pain caused by Oral Mucositis decreases the patients' quality of life. To preserve the quality of life during stem cell transplantation, more awareness has to be raised in prevention and therapy of Oral Mucositis.

The second part of the hereby presented work deals with the Epidemiology, preventive and therapeutic measures and the hereby caused costs of Oral Mucositis. We could show that more than half (58%) of the stem cell transplant patients were suffering from Oral Mucositis during their hospital stay; nearly half (47%) of the patients affected with Oral Mucositis suffered from a severe Oral Mucositis (Grade III, IV). After allogenic stem cell transplantation most patients suffered from Oral Mucositis between day 4 and 6 and day 14 and 15; in autologous patients the occurrence of Oral Mucositis accumulated between day 7 and 10. Age ≥ 65 years (69 % vs. 31 %, OR=3.78, CI 1.0 – 14.26, p=0.021), female gender (80 % vs. 47 %, OR=4.57, CI 1.01 – 19.67, p=0.035) and total body irradiation (77 % vs. 46 %, OR=3.75, CI 0.98 – 14.39, p=0.050) were identified as risk factors for the development of an Oral Mucositis; higher grades were found in patients with unrelated donors (2.63 vs. 1.29, p=0.014) and patients with a negative smoking history (2.69 vs. 1.77, p=0.036). Patients suffering from an Oral Mucositis needed more pain treatment (80 % vs. 32 %, p=0.001), intravenous opioids (24 % vs. 0 %, p=0.023) and liquid nutrition (51 % vs. 11 %, p=0.004). Autologous stem cell transplant patients with Oral Mucositis had €824 higher total treatment costs (nutrition, analgesia, anti-infectives) compared to patients without Oral Mucositis (p=0.037). In allogenic stem cell transplant patients higher costs were found in pain therapy (10 € vs. 2 €, p=0.034). During the hospital stay less than half of the patients (49%) were adherent to the prescribed amount of mouth rinses. Patients without

development of Oral Mucositis had a higher adherence to the oral care protocol (68 % vs. 35 %, p=0.027). 65% of the patients with low or missing adherence could not state a reason for their non-adherence. We could show, that Oral Mucositis is a frequent side-effect in stem cell transplant patients. The adherence of the patients regarding mouth rinsing is improvable. More attention should be paid to patients with unfavorable risk constellations to prevent the development of an Oral Mucositis and hereby reduce resource consumption and costs.

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II. Ergebnisse

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Burden of Oral Mucositis in stem cell transplant patients – the patients' perspective

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Burden of Oral Mucositis in stem cell transplant patients – the patients' perspective

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Abstract:

Purpose: Purpose of this study was to determine the impact of Oral Mucositis (OM) on health-related quality of life (HRQoL) and quality of life associated symptoms and functions in patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods: Prospective, non-interventional single-center observational study at a German tertiary teaching hospital. Inpatient allogenic and autologous stem cell transplant patients ≥ 18-year-old with high-dose chemotherapy. OM was assessed with the WHO Oral Toxicity Scale, pain according to the Numeric Rating Scale (NRS) and the performance status using the ECOG Score. QOL was captured with the EORTC QLQ-C30 and the QLQ-OH15 questionnaires.

Results: Forty-five stem cell transplant patients (20 autologous, 25 allogenic) were enrolled between August 2016 and February 2017. Twenty-six (58%, 95 % CI: 42% - 72%) patients developed OM (10 grade I, 4 grade II, 8 grade III, 4 grade IV). OM affected patients suffered more from pain, sore mouth and sensitive mouth. A lower physical functioning (34.5 vs 7.5, p=0.003) and a lower oral health related quality of life (24.3 vs 7.7, p=0.006) was found in patients with OM development. There was found a positive correlation between the grade of OM and the NRS-value (r=0.93, 95% CI: 0.89-0.96, p<0.001).

Conclusion: OM is associated with health-related quality of life and quality of life associated functions and symptoms. More research should be performed to find ways to prevent OM and to stabilize patients' quality of life during HSCT.

Keywords: cancer treatment, health-related quality of life, oral mucositis, hematopoietic stems cell transplantation, HSCT;

Introduction

One common side effect of chemotherapy and/or radiotherapy is oral mucositis (OM). OM is an inflammatory ulcerating process of the oral mucosa. Depending on the extent of OM, patients are limited in their ability to drink, eat, swallow and talk [1]. Patients with OM frequently suffer from pain, bleeding, weight loss and have an increased risk of infections [1,2]. They are often in need of liquid or even parenteral nutrition and a systemic pain treatment with opioids [3]. Furthermore, the duration of hospitalization was found to be longer in patients who develop OM [2].

The risk of developing OM is higher in certain therapeutic regimes, depending on the chemotherapy used, irradiation and dose. Patients receiving high-dose chemotherapy with or without total body irradiation (TBI) before hematological stem cell transplantation (HSCT) are at high risk of developing OM. Depending on the therapeutic scheme between 40% and 99% of the transplant patients suffer from OM [4-6]. Severe OM (grade III, IV) occurs in 10% to 67% of all autologous and allogenic patients [5,7]. Prior studies have shown that there is a statistically significant association between OM and health-related quality of life (HRQoL). Spielberger et al. showed that autologous stem cell transplant patients treated with palifermin, which lead to a reduction of the severity and duration of OM, had a better physical and functional well-being. Additionally, patients with no OM-affection reported less oral pain [8]. Another study in autologous patients performed by Sakellari et al. found that OM-affected patients had a lower total quality of life (QOL)-score and worse physical well-being [9]. Kim et al. conducted a study in autologous and allogenic stem cell transplanted patients treated with a recombinant human epidermal growth factor, which lead to a higher incidence but shorter duration of OM. Patients treated with this growth factor, who developed at least grade III OM, had less problems with swallowing and drinking [10]. Furthermore, Martinez et al. showed a relationship between a higher grade of OM and the presence of pain in hematological patients. Due to oral pain, patients were limited in their ability to drink and eat [11].

Stem cell transplant patients are already undergoing a very straining procedure – OM represents an additional factor affecting QOL in this period, which should not be neglected.

Hematopoietic stem cell transplantation is a fast-growing topic in modern oncology/hematology. Due to the most recent development in conditioning regimes the reduced-intensity conditioning (RIC) regimes further broaden the spectrum of patients eligible for allogenic stem cell transplantation. In a five-year period, from 2010 to 2014, the number of allogenic stem cell transplantations in Germany increased by 13.3%. Autologous stem cell transplantations grew by 18.7% in the same period. In total 15.9% more patients underwent transplantation in 2014 than in 2010 in Germany [12]. Across Europe, the increase was even higher - 22% in the five-year period (2010-2014), resulting in over 40,000 patients undergoing stem cell transplantation [13].

Therefore, in addition to the enhancements to the therapeutic regimens in stem cell transplantation, it is important to focus on the patients' burden during the therapy. Possible options to ease therapy-related symptoms (e.g. pain) and ensure a better quality of life during the stem cell transplantation should be discussed. Until now only limited data on the impact of OM on HRQoL in stem cell transplant patients has been published. Therefore, the objective of this non-interventional investigation with the character of a pilot study is to describe the relationship between OM and HRQoL in stem cell transplant patients with hematological malignancies to generate hypotheses for subsequent studies.

Study design / Patient characteristics

This study was designed as a prospective, non-interventional single center observational study. The study population consisted of hospitalized patients (≥18 years old) with a hematological or oncological disease, undergoing autologous or allogenic stem cell transplantation with high-dose chemotherapy. Exclusion criteria were ambulant patients or another current malignant disease.

Methods

Patients were consecutively enrolled in the study at a German tertiary teaching hospital from August 2016 to February 2017. Quality of life data was collected using in-person interviews, all other data was extracted from the patient's medical charts by one junior clinical scientist. Before being included in the study, patients were asked to sign an informed consent. The study was approved by the ethics committee of the Faculty of Medicine, Ludwig Maximilians University Munich.

Oral mucositis, pain and performance status

Oral mucositis was assessed according to the Oral Toxicity Scale of the World Health Organization (WHO-OTS) [14]. Current oral status according to the WHO-OTS and patients performance status using the Eastern Cooperative Oncology Group (ECOG) score were assessed three times a week [15]. Oral pain severity was documented at every assessment according to the numeric rating scale (NRS), which ranks "no pain at all" at 0 and "the worst pain possible" at 10 [16].

Quality of life

Quality of life was assessed using the German translation of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire with the QLQ-OH15 supplementary module [17]. The patient-reported outcome questionnaire EORTC QLQ-C30 consists of functional scales (e.g. cognitive functioning), symptom scales (e.g. pain) and a global health status, which equals a scale for the total QOL. The EORTC-QLQ-C30 is a validated, reliable and often used instrument [18]; the QLQ-OH15 is a new, but validated instrument for oral health related QOL in cancer patients [19]. In both questionnaires, all the scales range from 0 to 100. In the calculated scores (Global Health Status/QOL, oral health related QOL, Summary Score) a high score represents a high QOL. In the functional scales a high score represents a high/healthy level of functioning and in the symptom scales a high score represents a high level of symptomatology/problems. The in-person interview were conducted three days before HSCT, seven days after HSCT and 14 days after HSCT. The scientist was always available to conduct those interviews.

Because the duration of hospitalization in autologous transplant patients was rarely longer than 14 days after HSCT, only the allogenic transplant patients completed the questionnaire 3 times. Day 0 was defined as the day of transplantation.

Statistical analysis

All data was analyzed with the SPSS 24.0 statistical software package. For all calculations the patients were grouped according to their maximum grade of OM by that time point (7 days or 14 days). The results of the EORTC QLQ-C30 and QLQ-OH15 were calculated according to the official scoring procedure [20]. The EORTC QLQ-C30 Summary Score was calculated according to the scoring algorithm by Giesinger et al. of the EORTC Quality of Life Group [21]. We subtracted the patients' results in the second and third QOL-assessment from the baseline-value in order to evaluate the changes in QOL due to the transplantation procedure. The Mann-Whitney U-test was used to estimate differences between patients with OM compared to patients with no OM. The relationship between NRS-value and OM grade and the relationship between NRS-value, pain assessed by EORTC QLQ-C30 and the oral health related QOL were quantified using Spearman's rank correlation coefficient. The one-way Analysis of Variance (ANOVA) was used in order to calculate the relation between the functional scales and grade of OM. P-values <0.05 were considered statistically significant.

Results

45 patients (25 allogenic, 20 autologous) were enrolled in the study from August 2016 to February 2017. Two of these patients were unable to fill out the second QOL-questionnaire and one patient could no longer be followed three days after transplantation due to severely bad health status. The mean age of the patients was 52.6 years (range 18 – 74, SD 14.4) and 30 (67%, 95 % CI: 51% - 80%) of the patients were male. Seventeen (38%, 95 % CI: 24% - 54%) of all patients received total body irradiation. Of the allogenic patients 72% (95 % CI: 51% - 88%) were transplanted because of an acute myeloid leukemia (AML), 12% (95 % CI: 3% - 31%) because of a myeloproliferative neoplasm (MPNs), 8% (95 %

CI: 1% - 26%) because of a myelodysplastic syndrome (MDS) and 8% (95 % CI: 1% - 26%) because of an acute lymphoblastic leukemia (ALL). 50% (95 % CI: 27% - 73%) of the autologous patients underwent transplantation because of a multiple myeloma (MM), 40% (95 % CI: 19% - 64%) because of a lymphoma and 10% (95 % CI: 1% - 32%) because of a germ cell tumor (GCT). For more information about the patients see table 1.

Oral mucositis, pain and performance status

Twenty-six patients (58%, 95 % CI: 42% - 72%) developed an Oral Mucositis in the three weeks follow up period. Of these 26 patients, 10 (38%, 95 % CI: 20% - 59%) suffered from at most Grade I OM, 4 (15%, 95 % CI: 4% - 35%) developed OM up to Grade II, 8 (31%, 95 % CI: 14% - 52%) up to Grade III and 4 (15%%, 95 % CI: 4% - 35%) up to Grade IV. At the first QoL-assessment (Day -3) no patients suffered from OM.

Pain

Patients with OM had higher scores on the NRS-scale, progressively increasing with a higher grade of OM. We found positive correlation (r=0.93, 95% CI: 0.89-0.96, p<0.01) between NRS-value and OM grade (Figure 1). About one fifth (19%, 95 % CI: 7% - 39%) of the OM patients suffered from severe pain (NRS 7-10), 35% (95 % CI: 17% - 56%) from moderate pain (NRS 4-6) and 42% (95 % CI: 23% - 63%) from mild pain (NRS 1-3). Seventy-seven percent (95 % CI: 56% - 91%) of the OM-affected patients were treated with analgesia, and 23% (95 % CI: 9% - 44%) of the OM-affected patients were in need of intravenous opioids. There was a positive correlation between the QLQ-C30 pain value (r=0.72, 95% CI: 0.53-0.84, p<0.001) and the oral health related QOL (r=0.74, 0.55-0.85, p<0.001) on the second assessment (day +7) and the mean NRS-value during the first week. A higher grade of OM was associated with a higher risk of pain on the NRS-scale (r=0.80, 95% CI: 0.76-0.84, p<0.001).

ECOG

The mean baseline-ECOG-value (3 days before HSCT) in patients, who developed OM was comparable to the remaining patients (1.33 vs 1.38,

p=0.914). Statistically higher ECOG-values were found in OM-affected patients after day 3. For an overview of the ECOG-values during the first days of transplantation see Table 2. Because the first autologous patients were discharged on day +7, ECOG-values of the whole patient cohort were only compared until this assessment. Comparing only the allogenic patients on day +10 to +16, we found higher mean ECOG-values in OM-affected patients between day+10 and day+12 (Day 10-12: 2.25 vs 1.67, p=0.021; Day 13-15: 2.17 vs 1.67, p=0.058).

Quality of life

In the second QOL-assessment physical functioning (34.5 vs 7.5, p=0.003) decreased more in OM-affected patients and we found a signal of a higher decrease in social functioning (24.5 vs 5.3, p=0.097) of OM-patients (Table 3). Oral health related QOL (24.3 vs 7.7, p=0.006) was more strongly impaired in OM-patients and OM-affected patients had more problems with a sore mouth (-56.9 vs -1.33, p<0.001) and sensitive mouth (-43,1 vs -6.7, p=0.001).

While not all values are statistically significant, our data shows some evidence of difference while comparing mild (grade I, II, n=7) and severe OM (grade III, IV, n=10). Patients with grade III and IV OM had a higher decrease in the Summary Score (19.1 vs 7.5, p=0.172) and in the oral health related QOL (31.7 vs 13.7, p=0.070) and a higher increase in fatigue (-22.2 vs 4.8, p=0.049), pain (-56.7 vs -28.6, p=0.126), dyspnea (-10.0 vs 23.8, p=0.046), diarrhea (-33.3 vs 9.5, p=0.073) sticky saliva (-53.3 vs 0, p=0.032), sore mouth (-73.3 vs -33.3, p=0.017) and sensitive mouth (-66.7 vs -9.5, p=0.004).

Figure 2 shows the changes of the functional scales from the baseline-value to the second QOL-assessment. In the third QOL-assessment, patients with OM reported more problems with sore mouth (-37.0 vs -4.4, p=0.016), sensitive mouth (-18.5 vs 2.2, p=0.039) and pain (-42.6 vs 4.4, p=0.023) than patients with no OM. For an overview about the changes in the EORTC QLQ-C30 and QLQ-OH15 see Table 3.

Discussion

Data on burden of OM in stem cell transplant patients on QOL and pain is limited. This study is the first German study to show how OM influences patients' well-being in an already very straining situation. Overall, pain was found to be one of the major burdens associated with OM. Despite common pain treatments, patients reported high prevalence and levels of pain, which increased with higher grades of OM. In our patients QOL and QOL-associated functions (e.g. physical functioning) declined with OM, especially during the first week post transplantation. OM-occurrence was also associated with more fatigue, pain and a decrease in the oral health related QOL.

Our findings parallel those of Martinez et al., who showed that the higher the grade of OM, the higher the likelihood of patients developing oral pain [11]. Additionally, we found a positive correlation between a higher grade of OM and a more intense pain. Although nearly 80% of the patients in our study were treated with pain medication, including 23% with intravenous opioids, more than 50% of the patients still suffered from moderate or severe pain. Because of this still considerably high pain prevalence and severity, strategies to improve pain control in OM-affected patients should be discussed. Xing et al. showed that the treatment of pain caused by OM with transdermal fentanyl improved patients' quality of life [22]. Because of this finding, and the positive correlation found between the NRS-values and oral health related QOL in this study, we suggest that pain caused by OM has a huge impact on QOL of OM-affected patients. The correlation between NRS-values and pain assessed with EORTC QLQ-C30 supports the validity of our findings.

From 2000 until 2016 only four studies focused on the impact of OM on QOL of adult stem cell transplant patients. Two of these studies are European. One interventional study about the effect of palifermin on OM did not find an effect of the tested drug on OM and therefore could not find differences in QOL between patients with OM and no OM [23]. The other, non-interventional, study only described the QOL of all transplant patients and did not show differences in QOL between OM-affected patients and patients with no OM-development and

assumed OM to be the only cause for a QOL-impairment of stem cell transplant patients [9].

All QOL-associated functions were lower in our OM-affected patients or were lower in higher grades of OM, but only some were statistically significant. Like other studies before, we found a negative association between OM and physical functioning [24,8,25-28]. Similar results were seen by Öhrn et al., who found differences in all EORTC functioning scales but cognitive functioning [27]. Spielberger et al. and Elting et al. also found differences in functional well-being [8,25]. Three other studies showed a negative impact of OM on emotional functioning [24,26,28]. In our study population, the amount of pain, dyspnea and fatigue were also found to be higher in patients affected by OM. Higher pain-prevalence and increased fatigue were found by other studies [27-29]. Constipation and nausea and vomiting were not associated with OM; only small effects of OM on appetite loss were found. Nausea, as very frequent symptom after high-dose chemotherapy may mask the appetite loss caused by OM. Like Öhrn et al. showed, oral symptoms are closely related to quality of life [27]. In our study patients with OM had more problems with oral-health related symptoms, which negatively influenced oral health related quality of life.

While not all differences are statistically significant, we could show some trends while comparing mild to severe OM. A higher grade of OM was associated with more fatigue, pain and oral problems, a lower oral-health related QOL and QOL in total, and a lower physical functioning. Spielberger et al. found a correlation between physical, functional well-being and grade of OM and Cheng between physical and emotional well-being and grade of OM [8,26]. Because different assessment tools for QOL were used, these values are difficult to compare, but they all show similar findings. However, as fatigue is part of physical and functional well-being measured by the FACT-G questionnaire – our results are similar. It is possible that we were not able to find bigger changes because of the small sample size. More research is needed to further explore these trends.

The mean ECOG-values after transplantation were found to be higher in OM-affected patients, indicating a lower performance status for the patients with OM-development. Concerning the lower physical functioning indicated by OM-

affected patients in the EORTC QLQ-C30 questionnaire, both the patients' perspective and the measured ECOG-values by an observer show a decline in the OM-affected patients' physical condition.

Although data from nearly all patients in one large transplantation center has been collected for 7 months, the small sample size of this study is certainly a limitation. Future research should be done in a multicenter approach to achieve a larger patient cohort. Additionally, the supplementary module QLQ-OH15 we used only contains oral health related symptoms, but no oral functions like eating or talking. A validated module of the EORTC QLQ-C30 for assessing oral functions in hematological patients does not exist. Although OM was treated according to the same internal guidelines, the treatment was not identical for all patients. We can only suggest, that the patients were treated according to their individual requirements, which may limit the comparability of the patient collective.

Overall, the results of this single center study show the large impact of OM on QOL in stem cell transplant patients in routine care. Unique about this study is the assessment of QOL at certain points during the early period after stem cell transplantation and the evaluation of various aspects of QOL by using the EORTC QLQ-C30 and QLQ-OH15 in Germany. Our study may provide a baseline for more comprehensive non-interventional and interventional studies in OM in stem cell transplanted patients. QOL in stem cell transplants is already severely reduced due to the underlying disease and the procedure itself. Therefore, it is necessary to improve prophylaxis and treatment of preventable side effects like OM.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figure and table legends

Figure 1: Relationship of the NRS-value with OM grade
No OM n=276; OM grade I n=47; OM grade II n=18; OM grade III n=28; Om grade IV n=12;
[b] – the relationship between NRS-value and grade of OM was calculated with Spearman's Rank-Order correlation.

Figure 2: Changes in the EORTC QLQ-C30 functional scales from the baseline-value to the second QOL-assessment (7 days)
[c] – The one-way Analysis of Variance (ANOVA) was used in order to calculate the relation between the functional scales and grade of OM.
No OM n=25; OM grade I, II n=7; OM grade III, IV n=10.

Table 1: Patient Characteristics
Abbreviations: OM = Oral Mucositis; TBI = total body irradiation; HSCT = hematopoietic stem cell transplantation; AML = acute myeloid leukemia; DLBCL = diffuse large B-cell lymphoma; MDS = myelodysplastic syndrome; MPNs = myeloproliferative neoplasms; SD = Standard deviation.

Table 2: Comparison of the mean ECOG-values during the first week after transplantation
Abbreviations: nOM = patients with no Oral Mucositis development in this period; OM = patients with Oral Mucositis development in this period.

Table 3: Changes in the EORTC QLQ-C30 and QLQ-OH15
Abbreviations: nOM = patients with no Oral Mucositis development until the QoL-assessment; OM = patients with Oral Mucositis development until the QoL-assessment; HSCT = hematopoietic stem cell transplantation; SD = Standard deviation; QOL = quality of life.

Figure 1: Relationship of the NRS-value with OM grade

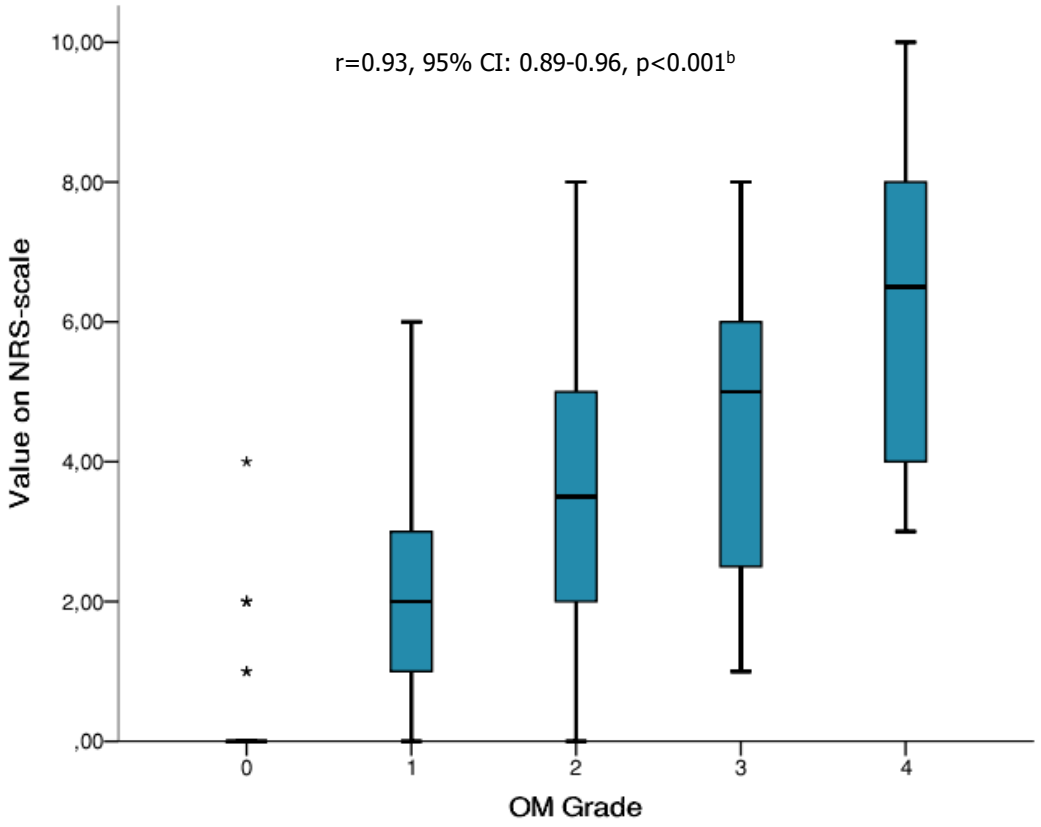

Figure 2: Changes in the EORTC QLQ-C30 functional scales from the baseline-value to the second QOL-assessment (7 days)

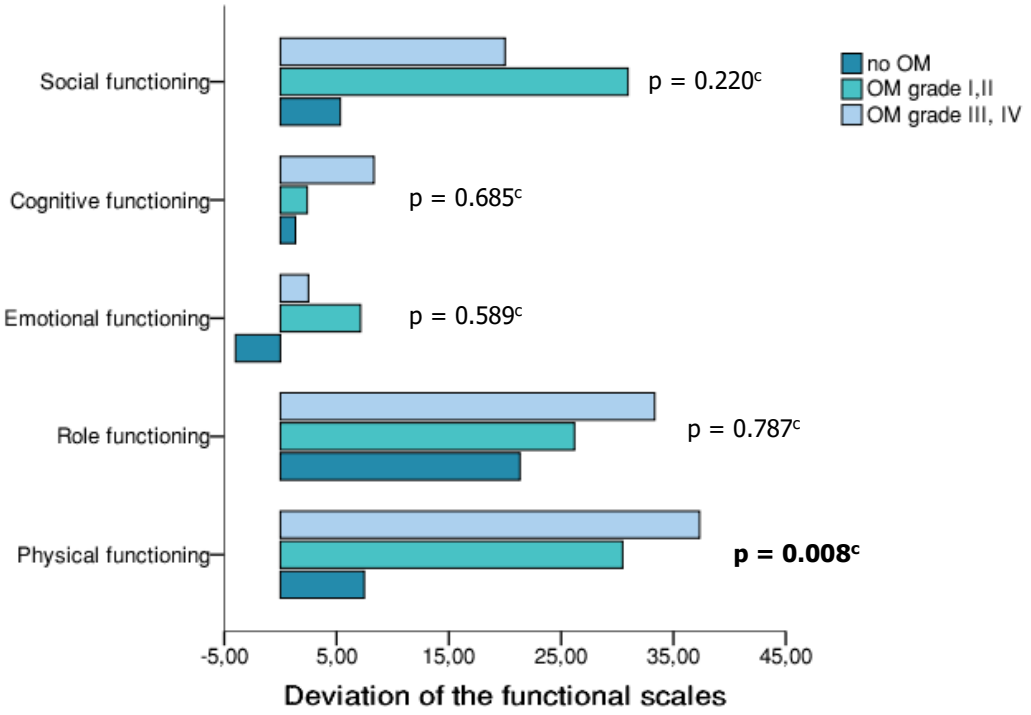

Table 1: Patient Characteristics

	n = 45
Sex – no. (%, 95% CI)	
Female	15 (33.3, 20-49)
Male	30 (66.7, 51-80)
Age (years) – mean (range, SD)	52.6 (18 – 74, 14.4).
HSCT – no. (%, 95% CI)	
Allogenic	25 (55.6, 40-70)
Autologous	20 (44.4, 30-60)
Oral Mucositis – no. (%, 95% CI)	26 (57.8, 42-72)
Grade I	10 (22.2, 11-37)
Grade II	4 (8.9, 3-21)
Grade III	8 (17.8, 8-32)
Grade IV	4 (8.9, 3-21)
Cancer diagnosis – no. (%, 95% CI)	
AML	18 (40.0, 26-56)
ALL	2 (4.4, 1-15)
Lymphoma	8 (17.8, 8-32)
DLBCL	4 (8.9, 3-21)
Mantle Cell L.	3 (6.8, 1-18)
Follicular L.	1 (2.2, 0-12)
Germ cell tumor	2 (4.4, 1-15)
Multiple myeloma	10 (22.2, 11-37)
MDS	2 (4.4, 1-15)
MPNs	3 (6.8, 1-18)
Cancer therapy – no. (%, 95% CI)	
Allogenic	
Myeloablative	4 (16, 5-36)
Reduced Intensity	21 (84, 64-96)
Non-myeloablative	0 (0, 0-0)
Autologous	
Melphalan	11 (55, 32-77)
BCNU, Thiotepa	3 (15, 3-38)
Cytarabin, Melphalan + TBI	3 (15, 3-38)
BEAM	2 (10, 1-32)
Carboplatin, Etoposid	1 (5, 0-25)

Table 2: Comparison of the mean ECOG-values during the first days after transplantation

	nOM	OM	p-value[a]
Number of patients	26	18	
Baseline (d-3)	1.38±0.70	1.33±0.77	0.914
Day 0 (≙HSCT)	1.73±0.60	2.00±0.91	0.198
Day 1-3	1.92±0.80	2.17±0.86	0.322
Day 4-6	1.92±0.63	2.33±0.69	0.058
Day 7-9	1.85±0.61	2.28±0.67	**0.040**

[a] - the Mann-Whitney U-Test was used to describe differences between patients with OM compared to patients with no OM-development.

Table 3: Changes in the EORTC QLQ-C30 and QLQ-OH15

	Baseline	Changes to Baseline: 7 days after HSCT			Changes to Baseline: 14 days after HSCT		
		nOM	OM	p-value[a]	nOM	OM	p-value[a]
Number of patients	45	25	17		15	9	
QLQ-C30 - mean (SD)							
Global Health Status/QOL	53.0±23.8	15.3±24.6	17.65±20.2	0.679	3.9±21.1	-2.8±11.0	0.432
QLQ-C30 Summary Score	67.0±16.2	7.5±15.9	19.1±15.0	0.838	14.2±26.5	17.0±29.1	0.387
Functional scales - mean (SD)							
Physical functioning	65.6±24.0	7.5±26.3	34.5±25.4	**0.003**	14.2±26.5	17.0±29.1	0.764
Role functioning	43.0±36.8	21.3±51.5	30.4±36.0	0.948	26.7±54.1	5.6±38.2	0.229
Emotional functioning	72.2±21.3	-4.0±24.8	4.4±28.0	0.624	-7.2±27.3	-7.41±13.5	0.952
Cognitive functioning	80.0±25.3	1.3±22.5	5.9±19.5	0.455	-6.7±16.4	-3.7±27.4	0.878
Social functioning	53.3±37.9	5.3±41.3	24.5±27.1	0.097	1.1±33.0	14.8±54.3	0.439
Symptom scales - mean (SD)							
Fatigue	49.6±32.7	-21.3±30.9	-11.1±30.2	0.267	-17.8±43.6	0±20.0	0.384
Nausea and vomiting	24.4±28.3	-20.0±37.9	-6.9±41.3	0.337	-23.3±58.4	1.9±31.7	0.293
Pain	22.2±28.0	4.0±28.6	-45.1±35.2	**<0.001**	4.4±39.6	-42.6±37.4	**0.023**
Dyspnea	31.1±32.1	5.3±28.3	3.9±37.0	0.913	13.3±27.6	0±55.3	0.288
Insomnia	34.1±36.6	-5.3±42.7	0±40.8	0.968	-15.6±37.5	-7.4±14.7	0.412
Appetite loss	42.2±41.7	-38.7±55.8	-15.7±47.3	0.183	-31.1±59.7	7.4±27.8	0.099
Constipation	10.4±23.4	12.0±28.7	3.9±20.0	0.328	6.7±31.4	3.7±11.1	0.906
Diarrhoea	28.9±37.3	-40±50.9	-15.7±52.9	0.123	-4.4±51.7	18.5±55.6	0.330
Financial	14.8±30.6	5.33±18.5	-2.0±27.6	0.613	6.7±22.5	11.1±33.3	0.966
QLQ-OH15 - mean (SD)							
Oral health related QOL	85.6±12.1	7.7±11.9	24.3±20.1	**0.006**	8.3±16.1	16.2±21.9	0.383
Symptom scales - mean (SD)							
Sore mouth	3.7±10.6	-1.3±20.4	-56.9±32.8	**<0.001**	-4.4±11.7	-37.0±38.9	**0.016**
Sticky saliva	22.0±32.1	-20.0±40.8	-31.4±54.6	0.368	-22.2±58.6	-3.7±65.5	0.459
Sensitive mouth	11.9±25.8	-6.7±23.6	-43.1±40.4	**0.001**	2.2±15.3	-18.5±55.6	**0.039**

[a] – the Mann-Whitney U-Test was used to describe differences between patients with OM compared to patients with no OM-development.

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Epidemiology, patient adherence and costs of oral mucositis in routine care in stem cell transplantation

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Epidemiology, patient adherence and costs of oral mucositis in routine care in stem cell transplantation

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Abstract

Purpose: Limited data about oral mucositis (OM) in stem cell transplant patients with underlying hematological disease is available in Germany. Purpose of this feasibility study was to determine incidence, treatment patterns, patients' adherence and costs of OM.

Methods: Prospective, non-interventional single-center observational study. Inclusion criteria: allogenic / autologous stem cell transplant patients ≥ 18 years, high dose chemotherapy. OM assessment: WHO Oral Toxicity Scale. Adherence was measured in patient interviews. Preventive and therapeutic measures were extracted from patients' charts.

Results: Forty-five patients (25 allogenic, 20 autologous) were enrolled. Twenty-six (58%) patients developed OM. (54% Grade I/II 46% Grade III/IV). Age ≥ 65 (31% vs 69%, p=0.021) was associated with a lower OM incidence. A positive history of smoking (1.77 vs 2.69, p=0.036) was associated with a lower OM grade, patients with unrelated donors (2.63 vs 1.29, p=0.014) were associated with higher OM grades and females (80% vs 47%, RR=1.71, p=0.035) with a higher incidence. OM-patients were less adherent to recommended daily mouth rinses (35% vs 68%, p=0.027). More analgesic treatment (80% vs 32%, p=0.001) and intravenous opioids (24% vs 0%, p=0.023) were prescribed in OM-patients. Total drug treatment and nutrition costs were 824€ (p=0.037) higher in autologous transplanted patients.

Conclusion: Initial risk and consecutive OM assessment, determination of patients' adherence, resource consumption and costs are prerequisites to evaluate OM care. In the best case, several centers will follow the same methodological approach and the collected data will serve as a basis for benchmarking analyses to optimize OM care where required.

Keywords: oral mucositis, hematopoietic stem cell transplantation, supportive cancer care, oncology

Introduction

In 2014 more than 40,000 stem cell transplantations were conducted in Europe, which is an increase of 22% compared to five years ago [1]. Chemotherapy and radiotherapy prior to stem cell transplantation have a significant negative impact on patient relevant clinical symptoms and side-effects like nausea, anemia, thrombocytopenia and mucositis [2,3].

In a previous study referring to a cohort of stem cell transplant patients with hematological disease and oral mucositis (OM) patients described significant pain values, loss of physical functioning due to OM. Subsequently OM is associated with a negative impact on the quality of life (QOL) [4].

Clinically OM can be associated with bleedings, infections and a loss of weight [5,6]. Severe OM can even cause changes and delays in treatment pattern and therefore endanger the success of cancer therapy [7,8].

So far evidence on the epidemiology of OM in stem cell patients with hematological diseases is limited. Published data on the incidence of OM in stem cell transplant patients varies between 40% and 96% [9,10]. Reasons for this range are different treatment patterns e.g. variations in conditioning regimes, but also different methodological approaches, e.g. applied OM assessment tools [11,12].

OM often requires liquid or parenteral nutrition, analgesic treatment and results in a longer hospital stay. Subsequently OM is associated with a higher consumption of resources and increased cost [13,6]. A Dutch / US-American study showed that an increase in one point on the peak Oral Mucositis Assessment Scale (OMAS) was associated with an increased cost of 25,405 US-Dollar in stem cell transplant patients [14]. A Brazilian study found an increased cost for parenteral nutrition and opioids due to OM in autologous ($US10,558) and allogenic patients ($US16,297) [15]. Until now there is limited data in Europe on the economic impact of OM in stem cell transplant patients –no German study has been published so far.

In order to manage therapy associated symptoms optimally, risk assessment, continuous symptom assessment, consecutive transparency on center specific epidemiology, on treatment patterns and on patients' adherence on prophylactic measures are fundamental, as well as transparency on resource consumption and economic consequences.

In a retrospective analysis covering the aforementioned areas we could identify only signals that the burden of OM is relevant from patients' and providers' perspective [17]. But due to the fact that routinely documented data has been either incomplete or not appropriately documented these results were associated by several uncertainties [16]. This underreporting in routine care was also reported by other studies dealing with OM [17,18].

Therefore, the purpose of this study was to determine within a prospective observational study the number of patients at risk for OM, incidence of OM, OM treatment patterns, patient adherence regarding mouth washes, resource consumption and the associated cost in routine care of stem cell transplant patients.

Patient characteristics

This feasibility study was designed as a prospective, non-interventional single center observational study in a German tertiary teaching hospital. As this study has been designed to observe patient care in routine care only a few inclusion criteria were defined: Adult patients (>18 years), hospitalized and undergoing autologous or allogenic stem cell transplantation due to a haemtological or oncological disease. Patients with a second current malignant disease were excluded from the study.

Methods

Patients were enrolled from August 2016 to February 2017. Data was collected by one clinical scientist; interviews were based on a pre-tested questionnaire. Informed consent was obtained from all individual patients included in the study. The study was approved by the ethics committee of the Faculty of Medicine,

Ludwig-Maximilians-University Munich, and was conducted in accordance with the 1964 Helsinki Declaration.

Incidence of Oral mucositis and risk factors for OM-development

Oral mucositis was assessed three times each week according to the Oral Toxicity Scale of the World Health Organization (WHO-OTS) [19]. The baseline performance status was captured with the Eastern Cooperative Oncology Group (ECOG) score three days before HSCT [20]. Patients were asked about risk factors for the development of OM such as a history of smoking, gender, age, history of oral lesions, former OM-episode, TBI, unrelated donors, consumption of alcohol three months before transplantation.

Patient adherence

Patients' level of awareness regarding oral complications was assessed by the EORTC QLQ-OH15 questionnaire [21]. The number of daily mouth rinses prescribed refer on internal care protocol according to the grade of OM (Grade 0 3-4x; grade I 4-6x; grade II, III, IV ≥6x). Compliance was ascertained by asking the patients three times a week. To standardize the assessment of compliance a questionnaire was developed and pre-tested.

Treatment patterns and economic consequences

Preventive and therapeutic measures were extracted from patients' charts beginning at the day of transplantation until discharge (autologous patients) or until 20 days after transplantation (allogenic). Cost of the administrated drugs were calculated according to the hospital pharmacy's cost catalogue.

Statistical analysis

Patients were grouped according to their maximum grade of OM by that time point (7 days or 14 days). Mann-Whitney U-test was used to describe differences in continuous variables between patients with and without OM development and Chi-square and Fisher´s exact tests were used for comparison of categorical variables. The relationship between duration of anti-infective therapy and OM grade was assessed using Spearman's Rank-Order correlation coefficient.

Significance level of 0.05 was used in all analyses. All data were analyzed using SPSS 24.0 statistical software package.

Results

Fifty-five patients underwent transplantation during the study period. Ten of those patients were not enrolled in the study due to following reasons: organizational issues (n=3), poor health status (n=3), difficulties in communication (n=2), rejection (n=1) and not meeting the inclusion criteria (n=1). Data from a sample of 45 patients (25 allogenic, 20 autologous) was analyzed. Mean age of the patients was 52.6 years (range 18 – 74, SD 14.4). Twenty-one (47%) patients had a history of smoking, and 3 (7%) patients were current smokers. Thirty-four patients (76%) consumed alcohol during the three months before transplantation. Thirteen (29%) patients had already suffered from OM in a prior therapy. In the 12 months before transplantation 20 (44%) patients reported oral lesions (38% gingivitis, 22% herpes blisters, 18% aphthous ulcers, 2% thrush). For more information about the patients see Table 1. Seventeen (38%) patients received total body irradiation. An overview of the administrated conditioning regimes is presented in Table 2.

Incidence of Oral mucositis and risk factors for OM-development

Twenty-six (58%) patients developed OM (10 Grade I, 4 Grade II, 8 Grade III, 4 Grade IV). Twenty seven percent of the patients (20% allogenic, 35% autologous) suffered from severe OM (Grade III, IV). For an overview about the distribution of the OM grades see Fig 1. The median day of onset was day 5 (mean 5.9, range 0-19, standard deviation (SD) 6.2) in allogenic patients and day 4 (mean 4.6, range 1-11, SD 3.3) in autologous patients. Most of the allogenic patients suffered from OM between day 4 and day 6 and day 14 and day 15 (32%), while most of the autologous patients suffered from OM between day 7 and 10 (50%). The highest mean grade of OM was found between day 6 and 9 in both allogenic (OM-grade ≥1.05) and autologous patients (OM-grade ≥1.9). Five (33%) allogenic patients were still suffering from OM after the end of the observational period (day +20) and three (27%) autologous patients were

discharged before the resolution of OM. For an overview about the course of OM see Fig 2.

Patients with a history of oral lesions had a lower incidence of OM (70% vs 48%, OR= 2.53, CI 0.73 – 8.71, p=0.142). Female patients developed OM more often than male patients (80% vs 47%, OR=4.57, CI 1.01 – 19.67, p=0.035). Patient who already developed OM in a former therapy (77% vs 50%, OR=3.33, CI 0.77 – 14.42, p=0.101) and patients with TBI (77% vs 46%, OR=3.75, CI 0.98 – 14.39, p=0.050) had a higher risk of developing OM. Patients < 65 years had a higher rate of OM (69% vs 31%, OR=3.78, CI 1.0 – 14.26, p=0.021) compared to older patients; OM affected patients younger than 65 years suffered from a higher grade of OM (2.36 vs 1.50; p=0.179) than older OM affected patients. No differences were found in either incidence (59% vs 56%, p=0.879) or OM-grades (2.05 vs 2.56, p=0.309) when comparing patients younger and older than 50 years. OM affected nonsmokers had higher OM-grades (2.69 vs 1.77, p=0.036) compared to former or current smokers. OM affected patients with unrelated donor had higher grades of OM (2.63 vs 1.29, p=0.014). Patients who consumed at least one glass of wine or beer daily in the last three months before transplantation had a lower OM-grade (1.67 vs 2.40, p=0.180).

Patients adherence

Three days before transplantation, 22% of the patients reported that they did not receive information about oral problems (the allogenic patients: 12%; autologous patients: 35%). Ninety-six percent of the patients who received information about OM and OM-treatment or prophylaxis were very satisfied with the received information.

During the hospital stay, 49% of the patients adhered to the prescribed number of mouth rinses. Patients with no OM development had higher adherence to the prescribed amount of daily rinses during the hospital stay (68% vs 35%, p=0.027). Twenty seven percent of the allogenic patients with OM development flushed correctly on all assessed days, which is a significantly less rate than the one among the patients with no OM development (27% vs 70%, p=0.036). Forty six percent of the autologous patients with OM flushed correctly on all assessed

days, whereas 67% of the patients with no OM flushed correctly (p=0.027). Looking at mouth rinsing during the first week after HSCT, 68% of the allogenic patients flushed their mouth correctly in this entire period, whereas 55% of the autologous patients flushed enough. Patients with grade I and grade II OM adhered more strictly to the prescribed amount of daily rinses than patients with grade III and IV OM (71% vs 42%, p=0.133). Of the patients who did not adhere to the daily amount of rinses, 15 (65%) patients could state a reason for not flushing the prescribed amount: 6 (40%) patients indicated the taste of the mouth wash would be the problem, 7 (47%) patients put the blame on their nausea, and 2 (13%) patients thought that the combination of the taste of the mouth wash and the nausea was the reason for their non-adherence.

Treatment patterns and economic consequences

OM affected patients needed more often analgesic treatment than those not affected by OM (80% vs 32%, p=0.001). Twenty percent of the OM affected patients needed NSAIDs for analgesia, compared to 32% among the patients without OM development (p=0.347). Sixty percent of the OM affected Patients used local anesthetics, whereas none of the patients without OM-development used local anesthetics (p=0.001). Patients with OM had a higher consumption of opioids (36% vs 11%, p=0.056) and intravenous opioids (24% vs 0%, p=0.023). Positive correlation was found between the grade of OM and the usage of opioids (r=0.63, p=0.003), intravenous opioids (r=0.54, p=0.013), local anesthetics (r=0.81, p<0.001) and the need of pain medication (r=0.71, p<0.001). Patients with OM needed fluid nutrition more often than patients without OM (51% vs 11%, p=0.004).

The following cost evaluation refers to patients with autologous stem cell transplantation. In the allogenic patient cohort (n=14), anti-infective treatment costs were not evaluable due to a relevant number of non-mucositis related fungal infections. In autologous patients with OM, the average treatment cost (nutrition, analgesic drugs and anti-infective drugs) was 824€ higher than in patients not affected by OM (p=0.037), see Table 3.

Discussion

More than half of the patients developed OM and a relevant part suffered from severe OM. Several risk factors like patients with unrelated donors, positive history of smoking, age ≥ 65 and female gender were found to have an influence on incidence or grade of OM. Patients with OM were less adherent to prophylactic measures. Less than half of the patients were completely adherent to prophylactic measures during the observational period. OM patients had a higher consumption of analgesic drugs. A higher total treatment cost was found in autologous OM-patients.

Incidence of oral mucositis and risk factors for OM development

The interpretation of our epidemiological data in the context of published data is limited because different OM assessment instruments like the WHO Oral Toxicity Scale or the Common Terminology Criteria for Adverse Events (CTCAE) V.4.03 of the National Cancer Institute (NCI) have been used. Taking into consideration studies which used the WHO-scale, like our study did, the incidence of OM in autologous patients varies between 56-87% [22,23]. With 55% of the autologous patients suffering from OM, our study population is located near the lower part of this range. Because of our mixed patient collective with different diseases and conditioning therapies a ranking of our study population is difficult. In the allogenic patients, the incidence of OM (60%) is positioned in the lower part of other recent studies - incidence between 55 – 96% [24,10]. We suggest that the lower incidence in our patient collective is caused by the limited usage (8%) of Methotrexate (MTX) for graft-versus-host disease (GVHD) prophylaxis. A similar incidence of OM was found in a systematic review by Chaudhry et al. for allogenic patients without MTX for GVHD-prophylaxis [11]. However, the studies Chaudhry et al referred to did not use consistent assessment instruments. Regarding the time course of OM, we found similar distribution of the OM-grades as in the study of Blijlevens (7 – 8.7 days vs 7 – 9 days) [25].

In order to verify the effect of risk factors on OM and to identify high-risk patients in routine care we conducted a risk factor analysis. We found a lower incidence in patients with previous oral lesions, but no difference in severity of OM. Dodd et

al. found lower grades of OM in patients with a history of oral lesions [26]. Like two other studies we found lower grades of OM in patients who had a history of smoking [27,28]. Patussi et al. suggest a hyperkeratosis of the oral mucosa caused by smoking as the reason for this effect [27]. Because an oral hyperkeratosis is not only caused by smoking, but also by frequent alcohol consumption, we suggested that frequent alcohol consumption may be a prognostic factor of OM, too [29]. We found slightly lower grades of OM in patients who had consumed at least one glass of wine / beer daily in the last three months before transplantation. Regarding age and the occurrence of OM two studies have been published. McCarthy et al. found higher grades and a higher incidence in patients ≥ 50 years receiving 5-fluoruracil [30]. Therefore, we evaluated patients over 50 years and found no difference in incidence and grades of OM.

Sonis et al found an increase in OM in younger oncological patients. Like Sonis et al we found a higher incidence and higher grades of OM in the younger population (<65). What might be explained by the fact of a faster proliferation of the epithelia [31]. Our data is in line with other studies, which found a higher incidence in female patients, patients with total body irradiation, and patients with a history of oral mucositis [6,32-34].

Patient awareness and adherence

Besides the underlying conditioning regimens and individual patient-related risk factors, insufficient adherence to preventive mouth washes could have an impact on OM development and severity grade of OM. Although the preventive effect of mouth rinsing on OM is not fully supported by evidence, intensive oral care has shown positive results regarding OM-incidence [35]. A group consisting of members of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT) highlighted the importance of basic oral care in patients undergoing HSCT and recommended the usage of an oral care protocol and bland rinses [36]. The first MASCC/ISOO-guidelines for OM even called basic oral care a “fundamental measure” for the prevention of OM [37]. An adherence of all patients during the entire

observational period of less than 50% could be an indicator of a lack of OM awareness. Patients with OM-development were more negligent with their amount of daily mouth washes than patients with no OM-development.

In patients following autologous transplantation adherence to mouth rinsing was slightly lower than in allogenic patients. More autologous patients told us they were not informed about oral complications, although all patients were routinely informed about the burden of OM and the importance of prophylactic measures before stem cell transplantation. Moreover, more than one third of the non-adherent patients could not report a reason for non-adherence. Good patient information and education is important in order to improve the understanding of the burden of OM and to enhance adherence for prophylactic measures.

Prevention, Treatment and Economic consequences

For OM prophylaxis OM-guidelines published by the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO) recommend the usage of recombinant human keratinocyte growth factor-1 (Palifermin) in autologous stem cell transplant patients with high-dose chemotherapy and total body irradiation. In patients undergoing HSCT low-level laser therapy is recommended as a prophylactic measure and patient-controlled analgesia with morphine shall be used to treat pain caused by OM. For patients with Oral care protocols and Cryotherapy for patients with high-dose melphalan is suggested in favor [38]. The guidelines of the German Society of Hematology and Oncology (DGHO) recommend frequent mouth rinsing with water or Sodium Chloride 0.9%. Oral care protocols and oral Cryotherapy for HSCT patients with high-dose Melphalan are suggest. No recommendation is given regarding the usage of low-level- laser therapy and Palifermin. If the patient is in need, systemic opioids are recommended for pain treatment of OM [39]. Until now recommendations on type of mouth rinse are limited due to a lack of (comparable) studies. Our center specific guidelines follow the DGHO guidelines. Subsequently most patients enrolled in this observational study rinsed their mouth with saline mouth-washes. For analgesia mainly local anesthetics added to the mouth rinse and opioids were used.

Patient controlled analgesia (PCA) and low-level-laser therapy were not performed.

In line with previous data we found an association between the OM-grade and opioid usage in stem cell transplant patients [15]. Additionally, we could show, that the number of patients, who received intravenous opioids and the general need for pain treatment correlated with a higher grade of OM. McCann et al. found a longer duration of antibiotic treatment and a higher number of patients with parenteral nutrition in OM affected Multiple Myeloma patients undergoing stem cell transplantation [22]. Similar to these findings, in our study population autologous OM-patients needed more often parenteral nutrition and treatment with antibiotics.

Regarding costs we focused exclusively on treatment costs (anti-infectives, analgesics, nutrition) from the hospitals' perspective. Average treatment costs were 824 Euros higher in OM patient following autologous transplantation. Due to a relevant number of allogenic patients with fungal infections in our patient cohort, the treatment data for anti-infective drugs in the allogenic patient cohort was not evaluable.

Similarly, two other OM-cost analyses found significantly higher costs in autologous OM-patients. They however analyzed the costs for the US setting and from a different perspective, respectively they referred to total hospital charges which also include additional days of hospitalization, lab testing etc. for inpatients [15,14]. Published economic studies for other countries concerning OM cost, are not transferable to German routine hospital care. No current data on resource consumption and cost of OM in stem cell transplant patients in Germany has been published so far.

Options for optimizing supportive care

Risk assessment before conditioning therapy could help to identify patients with a high risk of OM. These patients could be observed more closely and preventive measures could be adjusted.

Furthermore, OM should be assessed and documented routinely in a consistent way. The occurrence of OM could be identified early and appropriate measures

can be initiated. Also, the center specific incidence of OM could be determined and evaluated over time. If several centers would follow the same methodological approach, the results could be benchmarked against other centers for generating more knowledge about OM but also to compare the quality with the help of a larger cohort. Especially in patient cohorts with small numbers of patients, multi center comparisons can improve the significance of these evaluations. Therefore, a standardized assessment with a consistent instrument would be necessary. Moreover, the hereby generated data of multiple centers could be used for scientific purposes.

In order to show which costs and resources consumption are caused by OM, preventive and therapeutic measures have to be documented. In this context treatment patterns, which are used in routine care, can be documented and synchronized with the current treatment guidelines.

Both, the assessments of resource consumption and adherence has been time consuming. In the future, electronic patient charts might provide data to run these analyses continuously in an efficient way. For the collection of adherence data, patient tools such as self-reporting apps could be effective tools [40].

Limitations

The heterogenous patient collective with different malignancies and conditioning regimes and the small sample size are limitations of our study. A greater patient collective would have improved the possibility to identify and compensate for statistical outliers. Also, our study was performed in a single center, which limits the transferability of our study. A future study in a multicenter design based on the design and methods applied in this study would lead to stronger evidence and increase generalizability.

Conclusion

In conclusion in our study nearly sixty percent of the transplant patients suffered from OM, nearly half suffered from severe OM. We could show that a relevant number of patients have an increased risk of OM due to patient- and/ or therapy-related risk factors. Patients' adherence and awareness regarding mouth washes

could be improved as they might be a driver of OM development and higher severity grades.

In autologous stem cell transplant patients with OM we could show that OM is associated with higher treatment costs of about EUR 824. In consequence if the incidence and / or severity of OM could be improved, costs could be decreased simultaneously. Standardized routinely performed OM assessment and measuring patients' adherence would provide information for intra- and inter hospital quality assessments. In order to compare this data to other stem cell transplant units a standardized and reliable assessment with a consistent assessment tool is needed.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statement of human rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics committee of the Faculty of Medicine, Ludwig-Maximilians-University Munich, 345-16) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figure and table legends

Figure 1: Distribution of the severity of OM

Figure 2: Course of OM after HSCT in autologous and allogenic stem cell transplant patients. (Allogenic patients n=14; autologous patients n=11) Average duration of hospitalization for allogenic and allogenic HSCT patients is not equal, therefore the scale of the displayed days on the X-axis is different. Abbreviations: OM = Oral Mucositis; HSCT = hematopoietic stem cell transplantation; AML= Acute myeloid leukemia; ALL = Acute lymphoblastic leukemia; MDS = Myelodysplastic syndrome; Ly. = Lymphoma; MPNs = myeloproliferative neoplasms; MM = Multiple myeloma.

Table 1: Patient Characteristics
Abbreviations: OM = Oral Mucositis; TBI = total body irradiation; HSCT = hematopoietic stem cell transplantation; AML= Acute myeloid leukemia; MDS = Myelodysplastic syndrome; NRS = numeric rating scale; DLBCL = diffuse large B-cell lymphoma; MPNs = myeloproliferative neoplasms; SD = standard deviation; GvsHD = graft versus host disease; CyA = Ciclosporin; MMF = Mycophenolic acid; ATG = Anti-thymocyte globulin; TMP/SMX = Trimethoprim/Sulfamethoxazole; PBSCT = peripheral blood stem cell transplantation; BMT = bone marrow transplantation.

Table 2: Used conditioning regimes prior to HSCT
Abbreviations: TBI = Total body irradiation; BCNU = bis-chlorethylnitrosourea/Carmustine; FLAMSA = Fludarabine 30/4 / Ara-C 2000/4 / Amsacrine 100/4 / Filgrastim; Cy = Cyclophosphamide.

Table 3: Nutrition, treatment and cost of OM

Figure 1: Distribution of the severity of OM

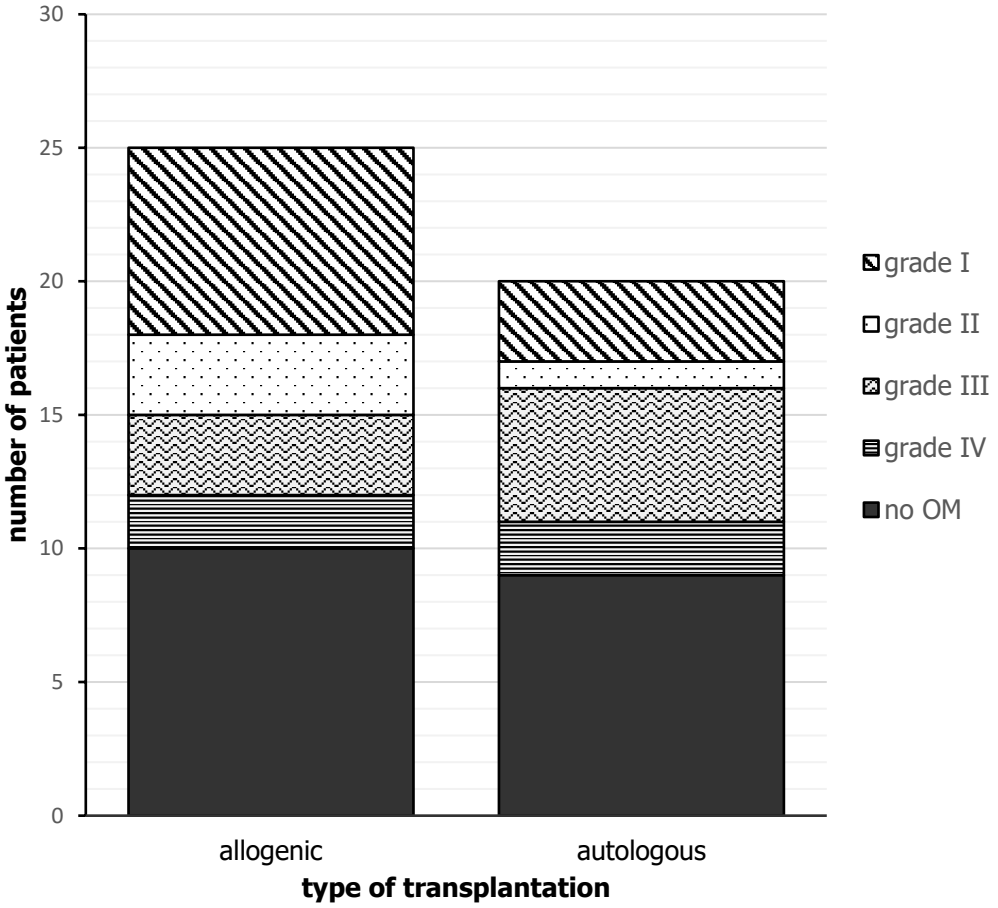

Figure 2: Course of OM after HSCT in autologous and allogenic stem cell transplant patients

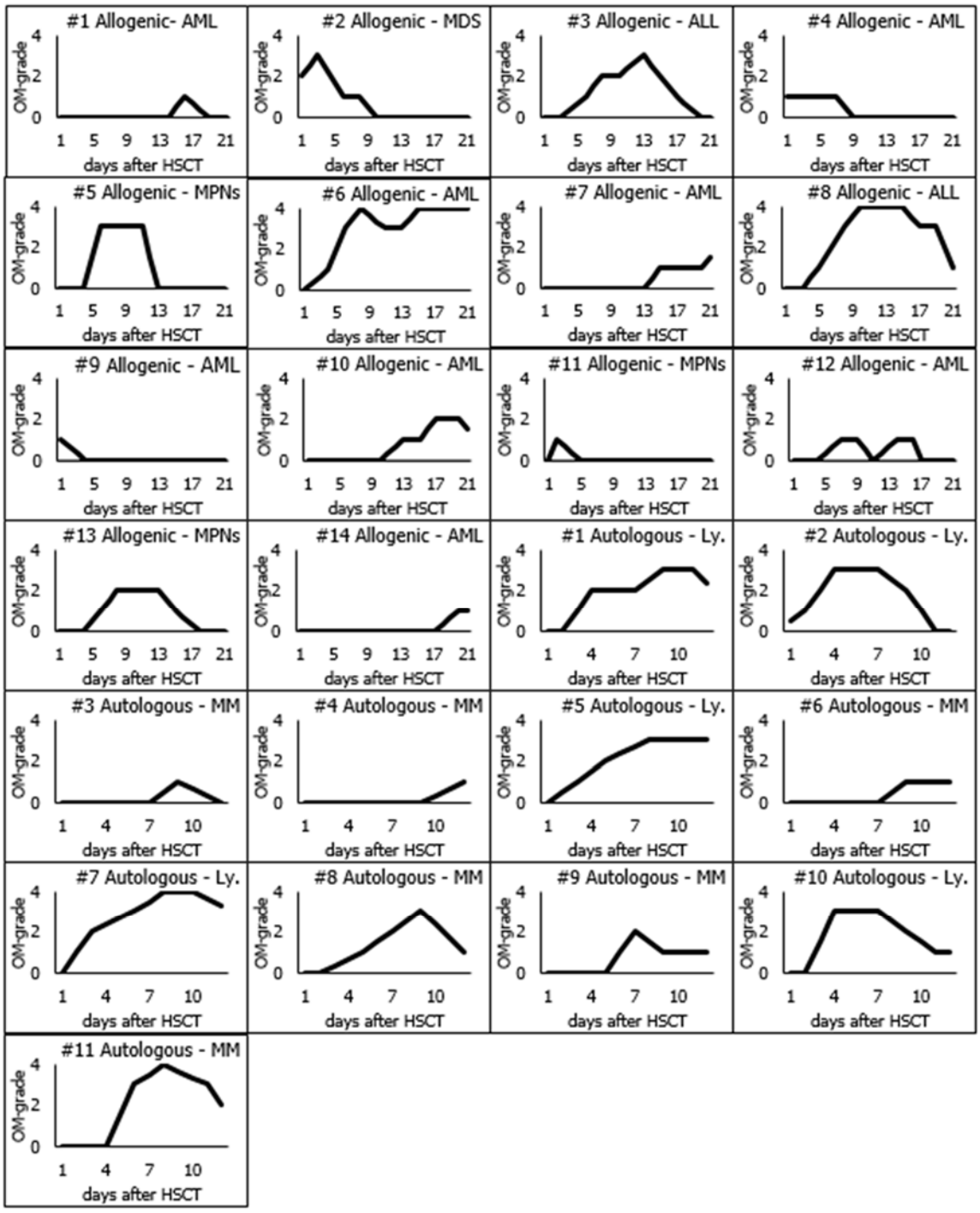

Table 1: Patient Characteristics

	No Oral Mucositis (n=19)	Oral Mucositis (n=26)	p - value
Sex – no. (%)			0.033[a]
Female	3 (16)	12 (46)	
Male	16 (84)	14 (54)	
Age (year) – mean (range, SD)	54.2 (23-74, 17.1)	51.4 (18-72, 12.3)	0.352[b]
HSCT – no. (%)			0.736[a]
Allogenic	10 (53)	15 (58)	
Autologous	9 (47)	11 (42)	
Baseline ECOG – mean (range, SD)	1.26 (0-3, 0.7)	1.42 (1-3, 0.8)	0.399[b]
BMI – mean (range, SD)	25.2 (19.8 – 37.2, 4.2)	25.7 (15.0 – 37.7, 5.2)	0.748[b]
Cancer diagnosis – no. (%)			0.217[a]
AML	9 (47)	9 (35)	
ALL	0 (0)	2 (8)	
Lymphoma	3 (16)	5 (19)	
Germ cell tumor	2 (11)	0 (0)	
Multiple myeloma	4 (21)	6 (23)	
MDS	1 (5)	1 (4)	
MPNs	0 (0)	3 (12)	
Cancer therapy – no. (%)			
Allogenic			0.075[a]
Myeloablative	0 (0)	4 (27)	
Reduced Intensity	10 (100)	11 (73)	
Non-myeloablative	0 (0)	0 (0)	
Autologous			0.218[c]
Chemotherapy	9 (100)	8 (73)	
Chemotherapy + TBI	0 (0)	3 (27)	
GvsHD-prophylaxis – no. (%)			0.472[c]
CyA/MMF/ATG	8 (80)	12 (80)	
CyA/MTX/ATG	0 (0)	2 (13)	
Tacrolimus/MMF	2 (20)	1 (7)	
Filgrastim – no. (%)	16 (84)	16 (62)	0.101[b]
Oral cryotherapy – no. (%)	0 (0)	2 (8) *[1]	0.221[b]
Mouth washes – no. (%)			1.000[c]
Saline mouth-wash Glandomed®	16 (84)	22 (85)	
Others (Caphosol, Dexpanthenol, mouthwashes based on etheric oils)	3 (16)	4 (15)	
Anti-infective prophylaxis – no. (%)			
Acyclovir	18 (95)	26 (100)	0.242[b]
Amphotericin B mouth wash/lozenge	9 (47)	13 (50)	0.863[b]
TMP/SMX	8 (42)	12 (46)	0.793[b]
Stem cells			
Allogenic – no. (%)			0.742[a]
Related Donor	4 (40)	7 (47)	
Unrelated Donor	6 (60)	8 (53)	
Transfused stem cells – mean (range, SD)			
PBSCT - $x10^6$ $cd34^+$-cells	7.4 (3.2 – 11.6, 2.7)	7.1 (1.4-11.2, 2.7)	0.680[b]
BMT - $x10^8$ TNC	2.7 (2.6-2.7,0.1)	2.7 (2.4 – 2.9, 0.2)	0.481[b]
Autologous – mean (range, SD)			
Transfused stem cells - $x10^6$ $cd34^+$-cells	6.8 (3.6 – 7.0, 3.0)	5.6 (3.0 – 7.3, 2.8)	0.196[b]

*[1] both of these patients were undergoing high-dose melphalan chemotherapy.

[a] Chi-square test, [b] Mann-Whitney U-test, [c] Fisher´s exact test

Table 2: Used conditioning regimes prior to HSCT

Autologous HSCT - – no. (%)	n=20
Cytarabine 3g/m², Melphalan 140mg/m² + 10Gy TBI	3 (15)
BCNU 400mg/m², Thiotepa 2x5mg/kg	3 (15)
BEAM (BCNU, Etoposide, Cytarabine, Melphalan)	2 (10)
Melphalan 100mg/m²	7 (35)
Melphalan 140/m²	4 (20)
Carboplatin 767mg/m², Etoposid 200mg/m²	1 (5)
Allogenic HSCT – no. (%)	n=25
FLAMSA-TBI (TBI 4Gy, Cy 60/2)	7 (28)
FLAMSA-BU (Busulfan 8x0,8mg/kg, Fludarabine 30/4, Cy 60/2)	3 (12)
FLAMSA (reduced) (TBI 4Gy, Cy 40/2)	1 (4)
Fludarabine 30/5, BCNU 150/2, Melphalan 110/1	6 (24)
TBI 4Gy, Cy 14,5/2, Fludarabine 30/5, Cy50/2	2 (8)
Cy 14,5/2, Fludarabine 30/5, Mel 110/1, Cy 50/2	2 (8)
TBI 2x4Gy, Fludarabine 30/4	3 (12)
TBI 3x4Gy, Cy 2x60	1 (4)

Table 3: Nutrition, treatment and cost of OM

Autologous patients	**no OM** n = 9	**OM** n = 11	**p-value[b]**
Nutrition			
Parenteral nutrition – no. (%)	0 (0)	3 (27)	0.098
Fluid nutrition – no. (%)	0 (0)	8 (73)	**0.001**
Cost (Euro) – mean (range, SD)	0 (0-0, 0)	23 (0-125, 45)	0.099
Analgesia			
Local Anesthetics (Tetracaine) – no. (%)	0 (0)	8 (73)	**0.001**
NSAID – no. (%)	2 (22)	1 (9)	0.425
Opioids – no. (%)	1 (11)	5 (46)	0.104
Intravenous Opioids – no. (%)	0 (0)	3 (27)	0.098
Cost (Euro) – mean (range, SD)	1 (0-7, 2)	15 (0-50, 18)	**0.006**
Anti-infectives			
Prophylaxis[1]			
Cost (Euro) – mean (range, SD)	9 (3-23, 7)	14 (0-48, 15)	0.819
Antiviral – no. (%)	0 (0)	3 (27)	0.098
Cost (Euro) – mean (range, SD)	0 (0-0, 0)	2 (0-48, 15)	0.331
Antibiotics – no. (%)	6 (67)	11 (100)	**0.043**
Cost (Euro) – mean (range, SD)	73 (0-186, 71)	157 (20-346, 105)	**0.044**
Antifungal – no. (%)	1 (11)	6 (55)	**0.048**
Cost (Euro) – mean (range, SD)	27 (0-240, 80)	723 (0-6240, 1897)	0.131
Cost (Euro) – mean (range, SD)	109 (4-430, 134)	896 (44-6473, 1938)	**0.053**
Total cost (Euro) – mean (range, SD)	110 (4–430, 134)	934 (47-6473, 1925)	**0.037**
Allogenic patients[2]	**no OM** n = 10	**OM[3]** n = 14	**p-value[b]**
Nutrition			
Parenteral nutrition – no. (%)	10 (100)	13 (93)	0.398
Fluid nutrition – no. (%)	2 (20)	5 (36)	0.414
Cost (Euro) – mean (range, SD)	473 (250-525, 85)	423 (100-525, 145)	0.829
Analgesia			
Local Anesthetics (Tetracaine) – no. (%)	0 (0)	7 (50)	**0.009**
NSAID – no. (%)	4 (40)	4 (29)	0.567
Opioids – no. (%)	1 (10)	4 (29)	0.280
Intravenous Opioids – no. (%)	0 (0)	3 (21)	0.127
Cost (Euro) – mean (range, SD)	2 (0-13, 4)	10 (0-93, 24)	**0.034**
Total cost (Euro) – mean (range, SD)	474 (263-527, 82)	433 (106-618, 151)	0.724

[b] Mann-Whitney U-test

[1] Prophylactic anti-infective treatment: Amphotericin B and/or Acyclovir and/or Trimethoprim/Sulfamethoxazole.

[2] Anti-infective treatment was not evaluable due to great differences between the allogenic patients in fungal infections.

[3] The number of allogenic OM-patients in this chart is cut down to 14, because of missing treatment-data of one patient.

III. Danksagung

An dieser Stelle möchte ich mich bei all denjenigen bedanken, die mich während meines Promotionszeitraums unterstützt und motiviert haben.

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IV. Publikationsliste

IV.1. Originalarbeiten

1. **Staudenmaier T**, Cenzer I, Crispin A, Ostermann H, Berger K.
Burden of oral mucositis in stem cell transplant patients-the patients' perspective. *Support Care Cancer*. 2018 May;26(5):1577-1584. doi: 10.1007/s00520-017-4000-5. Epub 2017 Dec 2.

2. Berger K, **Staudenmaier T**, Cenzer I, Crispin A, Strobach D, Ostermann H.
Epidemiology, patient adherence, and costs of oral mucositis in routine care in
stem cell transplantation. *Support Care Cancer*. 2019 Nov 5. doi: 10.1007/s00520-019-05107-2. [Epub ahead of print]

IV.2. Kongressbesuche und -präsentationen

1. **Staudenmaier T**, Ostermann H, Berger K.
The impact of oral mucositis on the quality of life of stem cell transplanted patients. *43rd Annual Meeting of the European Society for Blood and Marrow Transplantation*, Marseille, France, 26. – 29. March 2018: Abstract P378.
Bone Marrow Transplant. 2017 Jul;52(S1):S124-S516. doi: 10.1038/bmt.2017.134.

2. **Staudenmaier T**, Ostermann H, Berger K.
Oral Mucositis in Stem Cell Transplanted Patients.
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie, Stuttgart, Deutschland, 29. September-3. Oktober 2017: Abstracts. Oncol Res Treat 2017;40(suppl 3):1-308.

V. Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

„Orale Mukositis bei stammzelltransplantierten Patienten: Epidemiologie, Prävention, Therapie und Lebensqualität im klinischen Alltag.“

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 22.11.2020:

Tim Staudenmaier