
Shahrukh Hashmi  
Department of Adult Hematology and Stem Cell Transplantation, KFSHRC, Riyadh, Saudi Arabia

Marwan Shaheen  
Department of Adult Hematology and Stem Cell Transplantation, KFSHRC, Riyadh, Saudi Arabia

Salman Adil  
Aga Khan University Hospital, Karachi, Pakistan

Parvez Ahmed  
Quaid-e-Azam International Hospital, Islamabad, Pakistan

Syed Ahmed  
Department of Adult Hematology and Stem Cell Transplantation, KFSHRC, Riyadh, Saudi Arabia

See next page for additional authors

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Authors

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SPECIAL ARTICLE


Shahrukh Hashmi a,b,* Marwan Shaheen a, Salman Adil c, Parvez Ahmed d, Syed Ahmed a, Nour Ben Abdeljelil e, Amal Alabulwahab f, Amal Albeihany g, Saad Aladaama h, Murtadha Al-Khabori i, Salam Alkindi j, Fahad Almohareb a, Ahmed Alsaeed j, Amal Alseraihy k, Salem Alshemari l, Mouhab Ayas k, Naeem Chaudhri a, Waleed Da’na m, David Dennison i, Asma ElQuessar n, Alaa Elhaddad o, Ahmad Ibrahim p,q, Hasan Hashem m, Wasiel Jastaniah j, Hani Mawardi r, Amr Nassar s, Tariq Satti t, Lamia Torjemane e, Khalid Tabbara u, Hassan El Solh k, Bassim Albeirouti v, Mahmoud Aljurfi z

a Department of Adult Hematology and Stem Cell Transplantation, KFSHRC, Riyadh, Saudi Arabia
b Department of Medicine, Mayo Clinic, Rochester, MN, USA
c Aga Khan University Hospital, Karachi, Pakistan
d Quaid-e-Azam International Hospital, Islamabad, Pakistan
e Centre National De Greffe De Moelle, Tunis, Tunisia
f King Abdullah Medical City, Makkah, Saudi Arabia
g King Fahad Hospital, Madinah, Saudi Arabia
h King Fahad Specialist Hospital, Dammam, Saudi Arabia
i Sultan Qaboos University Hospital, Muscat, Oman
j King Abdulaziz Medical City-National Guard Hospital, Jeddah, Saudi Arabia
k Pediatric Hematology & Oncology, KFSHRC, Riyadh, Saudi Arabia
l Kuwait Cancer Control Center, Kuwait City, Kuwait
m King Hussein Cancer Center, Amman, Jordan
n Hematology, pediatric oncology, Ibn Rochd University Hospital, University of Hassan II, Casablanca, Morocco
o National Cancer Institute, Cairo, Egypt
p Makassed Hospital, Lebanese University, Lebanon
q Middle East Hospital, Lebanese University, Lebanon
r King Abdulaziz University, Faculty of Dentistry, Jeddah, Saudi Arabia
s Prince Sultan Military Medical Center, Riyadh, Saudi Arabia
t National Institute of Blood and Marrow Transplant, Rawalpindi, Pakistan
u Tabbara Eye Center, Riyadh, Saudi Arabia
v King Faisal Specialist Hospital & Research Centre, Jeddah, Saudi Arabia
w Hematology, Reykjavik University Hospital, Reykjavik, Iceland
x National Cancer Research Institute, Sydney, Australia
y Children’s Cancer Institute, Sydney, Australia
z King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia

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Hematopoietic cell transplantation (HCT) activity has increased significantly over the past decade with more than 65,000 HCTs being performed annually worldwide (both allogeneic and autologous) [1]. Roughly, half of these HCTs are undertaken in developing countries, particularly in...
South America and Asia. The Eastern Mediterranean (EM) region is composed of Afghanistan, Algeria, Bahrain, Cyprus, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, U.A.E., and Yemen Arab Republic. Within the EM, the Arab populations are the predominant group, but not the only group. Arabs have a relatively homogenous genetic inheritance compared to certain other ethnicities.

There is an increasing role of pharmacogenomics in cancer therapeutics [2,3]. It is imperative that the clinical community focuses on individualized treatments based on genetics rather than utilizing the one size fits all approach. The number of procedures has increased tremendously in the EM region over the past decade by 52.6% from 2006 to 2013 [4] (Table 1). Moreover, there has been a greater utilization of matched unrelated donors in some transplant centers within the EM region [5], which, when coupled with increased usage of peripheral blood stem transplantation, can lead to a greater incidence of graft-versus-host-disease (GVHD) [6].

As GVHD requires considerable expertise in diagnosis and management, its distinct features in different populations must be sought for proper management. Recent studies from Japan have implicated that SNP: single nucleotide polymorphisms in the REG3A gene (rs7588571) significantly influence the occurrence of chronic GVHD in adult Japanese recipients of HCT [7]. El-Beih et al. [8] evaluated single nucleotide polymorphisms at position 290 in the CYP3A4 gene in 33 HCT Arab recipients, and reported that those with CYP3A4 in AG or GG genotypes versus AA genotypes, showed a nonstatistically significant lower incidence of acute GVHD (0% vs. 18.5%; \( p = .28 \)) and severe oral mucositis (33.3% vs. 44.4%; \( p = .61 \)).

An international conference focusing solely on GVHD was undertaken in September 2018 in Riyadh, Saudi Arabia, where participants came from the majority of the EM region. Workshops on acute and chronic GVHD management were included in this conference and experts from many countries both within and outside the EM region (e.g. especially from the USA and the EU) participated. Given the paucity of the published data on GVHD management in the EM populations, opinion from GVHD experts was obtained during this GVHD conference portraying unique aspects of treatments in this population. Many distinct themes of GVHD in EM patients were discussed in this conference, including pharmacogenomics.

Herein, we describe the GVHD spectrum in the EM region. Then we summarize the currently available therapies for the management of GVHD in the EM region. We also describe the unique features of these treatments in the Arab populations along with future research priorities.

Table 1. Eastern Mediterranean Region Countries with HCT Centers.

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (in millions)</th>
<th>HCT center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>35.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Algeria</td>
<td>41.3</td>
<td>Yes</td>
</tr>
<tr>
<td>Bahrain</td>
<td>1.49</td>
<td>Yes</td>
</tr>
<tr>
<td>Djibouti</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>97.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Iran</td>
<td>81.1</td>
<td>Yes</td>
</tr>
<tr>
<td>Iraq</td>
<td>38.2</td>
<td>Yes</td>
</tr>
<tr>
<td>Jordan</td>
<td>9.7</td>
<td>Yes</td>
</tr>
<tr>
<td>Kuwait</td>
<td>4.1</td>
<td>Yes</td>
</tr>
<tr>
<td>Lebanon</td>
<td>6.08</td>
<td>Yes</td>
</tr>
<tr>
<td>Libya</td>
<td>6.37</td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>35.7</td>
<td>Yes</td>
</tr>
<tr>
<td>Oman</td>
<td>4.63</td>
<td>Yes</td>
</tr>
<tr>
<td>Pakistan</td>
<td>197</td>
<td>Yes</td>
</tr>
<tr>
<td>Qatar</td>
<td>2.63</td>
<td>Yes</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>32.9</td>
<td>Yes</td>
</tr>
<tr>
<td>Somalia</td>
<td>14.7</td>
<td></td>
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<tr>
<td>Sudan</td>
<td>14.5</td>
<td></td>
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<tr>
<td>Syria</td>
<td>18.2</td>
<td>Yes</td>
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<tr>
<td>Tunisia</td>
<td>11.5</td>
<td>Yes</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Yemen</td>
<td>28.2</td>
<td></td>
</tr>
</tbody>
</table>

Note. HCT = hematopoietic cell transplantation.

Results from the workshop and the expert panel discussions conducted during the 2018 GVHD symposium indicated the following key issues:

1. GVHD prophylaxis with the regimen of four full doses of methotrexate (MTX) was noted to be toxic and poorly tolerated in several EM centers. Clinical experience at the inception of HCT in Saudi Arabia three decades ago has inferred a higher transplant-related mortality with the full four-dose regimen of MTX, thus currently many centers affiliated with EMBMT give three doses of MTX as GVHD prophylaxis. However, this is anecdotal information and sophisticated studies are needed to delineate exact toxicities and efficacies of GVHD treatments.

2. Serotherapy with antithymocyte globulin (ATG) is a feasible and available option for GVHD prophylaxis in most EM countries, however, its exact dose is controversial and different centers are using different formulations with various dosages in allogeneic HCTs. Those centers
within the EM region which perform matched unrelated donor HCTs are routinely using ATG for GVHD prophylaxis. Rabbit ATG is the preparation that is most widely used in EM countries for GVHD prophylaxis, however, the dosage differs based on the disease and the donor.

3. The presentation of acute GVHD in EM populations may also differ compared to the series reported from North America and Western Europe (e.g. some centers observed a higher frequency of isolated gut GVHD and others commented on cutaneous acute GVHD having a more aggressive course with or without the involvement of the gastrointestinal tract). This may reflect a possible difference in the pathogenesis of the disease given differences in both HLA and minor antigens between the donor-recipient pairs.

4. Extracorporeal photopheresis is not available in most of the countries of the EM region. Its prohibitive cost and logistics are the main barrier of its implementation in the EM region. It is currently only available at selected centers.

5. Management of GVHD in the EM region should be focused on very aggressive prevention and early treatment strategies, as approximately half of the allogeneic HCTs being conducted in the EM region are for nonmalignant indications including primary immunodeficiency, hemoglobinopathies and for bone marrow failures, in contrast to the USA and the EU, where the majority of allogeneic HCTs are being performed for malignant conditions.

6. ATG- or alemtuzumab-based GVHD prophylaxis may have a strong role in the prevention of GVHD in sickle cell anemia patients undergoing HCTs. This strategy is being utilized at select HCT centers in EM countries.

7. The absence of multidisciplinary GVHD clinics is a great barrier towards efficient long-term care of chronic GVHD patients. Currently, only a few fully functional multidisciplinary GVHD clinics exist in EM countries, which include oral surgery/dentistry, gynecology, physical therapy, pulmonology, and dermatology as the specialties evaluating GVHD patients in this clinic.

8. With a high rate of marital consanguinity and homogenous genetic inheritance, pharmacogenomics research specific to EM populations should be a priority and a step towards personalized medicine. Currently, very scant published literature exists with respect to the pharmacogenetic variations in Arab populations.

9. Utilization of machine learning methods (artificial intelligence) for both prognostication and GVHD prevention (donor-recipient matching) may be a cost-effective approach in the long run and should be considered to evaluate various aspects of GVHD [9,10]. Protocols that optimize the use of cost-effective interventions should be developed especially in the steroid-refractory setting.

10. There is a paucity of GVHD expertise in the EM region. Training and education among hematologists and trainees should be essential in the institutions performing allogeneic HCTs. Ideally, trainees in hematology and BMT fellowship programs should have exposure to inpatient and outpatient rotations for acute and chronic GVHD, respectively.

11. Lack of randomized trials in GVHD management from the EM region calls for an urgent investment of resources towards GVHD treatment and prevention using novel agents. Though retrospective studies on GVHD are available in literature, no investigator-initiated clinical trials on GVHD have been published in the peer-reviewed journals from the EM region. Pharmacogenomics and pharmacometabolomics research must be undertaken in GVHD given a unique population.

12. GVHD care is an important HCT cost item. Many centers are operating in low- to middle-income countries, and accordingly prevention of this potential complication is an important priority particularly, and as mentioned earlier, a substantial proportion of HSCT procedures are done for non-neoplastic indications.

Our review and expert opinion indicate some differences in outcomes in patients being transplanted in the EM region compared to the USA and EU. A paucity of published literature is observed in GVHD management from the EM countries. This paper can be a guide towards the pharmacogenomics approach in GVHD patients, especially with MTX and CNI: Calcineurin Inhibitors until pharmacogenomics data originating from countries within the EM region is generated. Utmost efforts should be undertaken towards a personalized medicine approach in GVHD patients, in addition to diverting resources towards education, training, and research within EM countries with the rise of HCT activity in this region.

Disclosures

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Authorship Contributions

All authors contributed to all sections of the manuscript and agree for the submission of the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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