HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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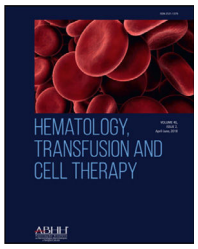

PEDIATRIC PRESENTATIONS

Sp01

INFLAMMATION AND CANCER

Jean-François Rossi

Normal inflammatory response represents the initial phase of the immune response. This normal or "good" inflammatory response is transient, followed by a return to the normal status. Dysregulated or "bad" inflammatory responses are observed in inflammatory, infectious diseases and cancers, and can be characterized by inappropriate levels of inflammatory markers, speed of generation, and major site of production, such as a vital organ. Chronic or smoldering inflammation is associated to cancer initiation as observed in lung, gut, or cervical cancers and with obesity, which is associated to multiple factors such as dysmetabolism, gut dysbiosis, immune dysfunction and immune exhaustion. Inflammation is also associated with cancer promotion, proliferation, metastasis, and thrombosis risks. Due to the persistent and high inflammatory response, immune tolerance is also amplified and leads to immune resistance. Thus, to amplify cancer cell control, the dynamics of the inflammatory response must be evaluated to determine its negative impact and to open a more personalized therapy including the return to a normal inflammatory/immune response. To optimize anti-IL6 therapies, we developed an algorithm to mathematically model inhibition of IL-6 activity in the presence of either siltuximab (anti-IL-6), tocilizumab (anti-IL-6R), or both. By analyzing data in COVID-19 cytokine storm, biological efficiency was not reached showing that there is a need to optimize anti-IL6/antiIL6R therapies which were not correctly used. We also retrospectively analyzed data from the randomized study with siltuximab in Castleman disease, and open new possibilities in cancer, particularly for immune therapies.

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2531-1379/

Sp02

NEW ADVANCES IN PEDIATRIC ACUTE MYELOID LEUKEMIA

Özlem Tüfekçi

Pediatric acute myeloid leukemia (AML) accounts for ~20% of childhood leukemias and has been a clinical challenge due to its heterogeneity, high relapse rate and therapy-related toxicity. As compared to 90% overall survival in childhood acute lymphoblastic leukemia, event-free survival and overall survival remain suboptimal at 45% and 65%, respectively at three years and nearly half of children will relapse. Treatment protocols for pediatric AML have converged to a standard that includes four or five cycles of intensified myelosuppressive chemotherapy with cytarabine and anthracyclines followed by hematopoietic stem cell transplantation (HSCT) for a subgroup of patients. It is clear that the ceiling to further intensification of standard chemotherapy has been reached in AML, urgently necessitating novel therapeutic strategies. Recent developments in comprehensive mutation testing and integration of data from adult clinical trials led physicians try novel agents in pediatric AML patients especially in the relapse/refractory setting. In this context major treatment modalities and novel drugs in childhood AML include immunotherapy including drug-antibody conjugates and chimeric antigen receptor T-cell (CAR-T cell) therapy, epigenetic modifiers, tyrosine kinase inhibitors,and other novel agents. The addition of gemtuzumab ozogamicin and FLT3 inhibitors to some standard chemotherapy protocols has been becoming a standard of care in treatment of pediactric AML. Besides, major advances have also been achieved in acute promyelocytic leukemia (APL). The combination of ATO and ATRA without chemotherapy is now the standard chemotherapy for adults that are in the standard risk. Based on these findings; recent trials on pediatric APL patients aim to use ATRA plus ATO while minimizing the use of chemotherapy.

Recently, considerable progresses have been achieved in defining the molecular landscape of AML that lead scientists to discovery of novel drugs. There have been numereous ongoing studies on new therapeutic agents for AML, and

some of them have already been included in the standard treatment protocols, but further studies on other new agents are needed to determine their efficacy in children.

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Sp03

MEDICAL TREATMENT IN HODGKIN LYMPHOMA

Nilgun Kurucu

The treatment of HL has been designed according to risk stratification. Risk stratification is based on presenting features at diagnosis. Stage of disease, presence of bulky disease, presence of B symptoms, and number of involved nodes are the parameters of risk determination. Low risk group includes stage IA and IIA disease with no tumor bulk and no extranodal involvement. Stage IA and IIA with bulky disease or extranodal involvement, and stage IB and stage IIIA are defined as intermediate risk. Stage IIB with with bulky disease or extranodal involvement, IIIB and IV diseases are in high risk group. Treatment of HL in children consists of combined modality treatment including multiagent chemotherapy and low dose involved field radiotherapy. Modern therapy of HL can be based on both risk group and response (Table I, II, III). Standard chemotherapy in Hodgkin disease is ABVD or MOPP derivatives. Adriamycine, Dacarbazine, Bleomisin and Vinblastin are the major drugs of ABVD derivative protocols. MOPP derivatives include generally cylophospamide, vincristine, procarbazine, prednisolone. Hodgkin lymphoma is a radiosensitive disease. In general, doses of 15 to 25 Gy are used with modification based on patient and disease characteristics. In combined modality era, the extended treatment volumes are no longer needed. The Involved fields reduce the exposure of normal tissue and the late side effects by not reducing local control rate. The implementation of more tailored fields is a progress toward this goal, treating only the individual lymph nodes with a margin for microscopic disease. This, in conjunction with modern imaging, will continue to reduce exposure of normal tissue to radiation while maintaining equivalent local disease control rates. In some recent trials, radiotherapy was omitted in localized low risk disease and early responder patients.

Combined modality treatment will result in very high cure rates (Table I, II, III). The treatment results in children with early stage disease are perfect. Disease-free survival and overall survival reach up to 95% and 100%, respectively. About ten to twenty percent of advance stage patients may relapse. Since the prognostic outlook and life expectancy of HL have shown significant progress over the last decades, the quality of life and prevention of late side effects have gained considerable importance. Balance ensuring the best opportunity for long-term disease-free survival and the lowest risk of severe treatment toxicity should be achieved.

Table I. Treatment of Low Risk Group

Low Risk Studies	Treatment		EFS
POG 8625	6 MOPP/ABVD	+None	83%
(1986-92, 247 pts)	4 MOPP/ABVD	+LD-IFRT	91%
CCG 5942	4COPP/ABV	+ None	89%
(1995-98, 826 pts)	4COPP/ABV	+ LD-IFRT	100%
COG 9426	2 DBVE	CR ⇨ +LDIFRT	87%
(1996-2000, 294 pts)		<CR ⇨ +2DBVE+ LDIFRT	85%
COG AHOD0431	AVPC	CR ⇨ +None	78%
(2006-2009, 278 pts)		<CR ⇨ +LDIFRT	83%
MDH90	4 VBVP	CR ⇨ +IFRT	90%
(1990-2008,202 pts)	4 VBVP	<CR ⇨ +2-4 OPPA +IFRT	78%
GPOH-HD 2002	2 OEPA(M)/OPPA(F)	CR ⇨ +None	93%
(2002-2005,573 pts)		<CR ⇨ +LD-IFRT	92%

Table II. Treatment of Intermediate Risk Group

İntermediate Risk Studies	Treatment		EFS
CCG 5942	6 COPP/ABV	⇨ + None	78%
(1995-98,834 pts)		⇨ + LD-IFRT	84%
POG 9425	3 ABVE-PC	RER ⇨ +LDIFRT	86%
(1997-2001, 219 pts)		SER ⇨ +2ABVE-PC+ LDIFRT	88%
AHOD0031	2 ABVE–PC	RER ⇨ CR +2ABVE-PC + None	84%
(2002-2009, 1734)		RER ⇨ CR + 2ABVE-PC+ LDIFRT	88%
		RER ⇨ <CR +2ABVE-PC+LDIFRT	87%
		SER ⇨ +2DECA+2ABVE-	79%
		PC+LDIFRT	75%
		SER ⇨ +2ABVE-PC+LDIFRT	
GPOH-HD2002	2 OEPA/OPPA+4COPP/COPADC +SDIFRT		88%
(1997-2001, 219 pts)			

Table III. Treatment of High Risk Group

High Risk Studies	Treatment		EFS
POG 8725 (1987-92, 183 pts)	4 MOPP/4ABVD	CR ⇨ +None ⇨ +LDTNI	82% 87%
CCG 5942 (1995-98, 826 pts)	COPP/ABV+CHOP+Ara-C/VP-16	⇨ +None ⇨ +LDIFRT	81% 90%
POG 9425 (1997-2001, 219 pts)	3 ABVE-PC LDIFRT	RER ⇨ +LDIFRT SER ⇨ +2ABVE-PC+	88% 82%
CCG 59704 (1999-2002, 99 pts)	4 BEACOPP/ABVD +4BEACOP+LDIFRT	RER (F) ⇨ +4 COPP/ABV RER (M)⇨+2ABVD+ LDIFRT SER ⇨	94%
COG AHOD0831 (2009-2012, 166)	2ABVE-PC PC+LDIFRT PC+IV+LDIFRT	RER ⇨ +2ABVE- SER ⇨ +2ABVE-	84% 73%
GPOH-HD2002 (2013-2020, 77pts)	2 OEPA/OPPA+4COPP/COPADC +SDIFRT		87%

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Sp04

LATE EFFECTS OF CHILDHOOD CANCER: THE FOUNDATION FOR RISK-STRATIFIED PEDIATRIC CANCER CARE LONG TERM

Melissa M. Hudson

Progress in biology and therapy for pediatric cancers has produced a growing population of long-term (exceeding 5 years) cancer survivors who are at increased risk for morbidity and premature mortality related directly to the cancer itself, to pre- and co-existing comorbidities, and to exposure to cancer treatment modalities. Consequently, cancer survivors represent an important group that may benefit from risk assessment, disease prevention services, and health promotion counseling. Risk-based survivor care that includes tailored screening, surveillance, and prevention based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and co-morbid health conditions is recommended for all survivors. To optimize risk-based survivor care, several groups have organized health screening guidelines based on evidence from the literature linking specific therapeutic interventions with late treatment complications.

In addition to evidence-based guidelines, optimal survivorship care requires a comprehensive, multidisciplinary care infrastructure or model of care. A variety of models of survivorship care have been described across practice settings including academic models, community practice models, and shared-care models. The shared-care model, which features co-management of survivors by oncology and primary care providers, has been promoted for its facilitation of survivor access to cancer- and non–cancer-related preventive services. A risk-stratified approach has been recommended in defining the ideal model of follow-up care for specific survivors. Risk factors typically considered in these models include treatment intensity, risk of recurrence, persistence of moderate to severe toxicity of therapy, risk of serious physical late effects, and psychosocial status.

To facilitate care coordination among oncologists and community providers, the use of a written treatment summary and care plan is recommended to communicate the survivor's health status, provide a care roadmap to ensure survivor-appropriate services, and clearly delineate provider roles. However, adherence to this recommendation by oncology providers remains suboptimal because of the significant time and resource barriers involved in organizing survivorship care plans. Identification of the essential components of survivorship care plans, which may vary across health care settings, is important to facilitate their widespread adoption. The integration of automated, programmable applications within existing electronic health record systems may expedite the development of care plan summaries in the future. To enhance awareness of survivorship health issues, educational efforts must be expanded to target not only oncology providers, but also practicing clinicians, graduate medical trainees, and survivors.

Continued follow-up during adulthood is essential to accurately characterize very late cancer-related sequelae and determine if complications resulting from cancer therapy will be exacerbated by the organ dysfunction associated with aging. In this way, late health outcomes research plays a critical role in refining screening/surveillance recommendations and guiding the development of preventive and remedial interventions to preserve health.

This presentation will review the scope of long-term health effects after pediatric cancer, the challenges in coordinating long-term survivor care, health screening guideline resources available to facilitate survivor care, and the impact of late health outcomes research among adults treated for childhood cancer.

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Sp05

UPDATE ON FERTILITY PRESERVATION

Murat Sönmezer

Over the past 50 years, there has been a remarkable improvement in the cancer survival rates due to significant progress in the diagnosis and treatment. However, multi–agent chemotherapy regimens and/or radiotherapy, and hematopoietic stem cell treatments are associated with significant long–term sequels such as growth disorders, cardiovascular problems, neurocognitive abnormalities, secondary malignant tumors, and reproductive failure. Cytotoxic therapy has also been used in some non-malignant hematologic, immunologic, and genetic diseases, which are resistant to standard treatment modalities. Moreover, gonadal surgery for benign gynecological lesions including endometriomas may be associated with decreased ovarian reserve, even can result in a permanent ovarian failure especially if the disease is bilateral. It was projected that in 2020, there would be approximately 90.000 new cancer cases in adolescents and young adults, on the other hand overall cancer mortality declined by 1% annually, from 2008 to 2017 among all age and sex groups [1]. As a result of the increasing number of cancer survivors, a strong focus has been placed on the delayed effects of cancer treatments which can all affect future quality of life of the patients.

When selecting the most optimal option to preserve fertility one should analyze all possible confounding factors such as age of the patient, available time before cancer treatment, ovarian reserve, the type and duration of chemotherapy and/or radiotherapy, and couple status. There are currently various established and non-established techniques for fertility preservation performed worldwide. Embryo cryopreservation has long been practiced with high success rates which is quite similar to outcomes using fresh embryo transfer. Likewise, with the advent of modern freezing technologies including vitrification, the success rates with oocyte freezing have also remarkably increased. Before oocyte or embryo cryopreservation at least 2 weeks is required for ovarian stimulation before oocyte retrieval. For estrogen sensitive tumors including breast and endometrial cancers, safer ovarian stimulation protocols incorporating letrozole were defined with high success rates. Patients undergoing pelvic radiotherapy laparoscopic ovarian transposition can be performed, however the success rates vary between 16-90%. Ovarian tissue cryopreservation and transplantation is among one of the key components of available fertility preservation techniques with more than 200 reported livebirths worldwide. Transplantation of frozen thawed ovarian tissue is not only a viable option to achieve pregnancy, but it also enables resumption of reproductive functions by producing hormones that has a substantial impact on the quality of life of the patients suffering premature ovarian failure. One of the most important advantages of ovarian tissue freezing is that there is no need to delay cancer treatment since ovarian stimulation is not required. Although various methodologies have been tested in many animal and human studies for ovarian tissue freezing, until recently, this procedure has been classified as “experimental” as the precise methodology has not yet been established. However, with increased clinical success together with increasing number of healthy live births in recent years, ovarian tissue freezing is now considered as an "acceptable" method for fertility preservation. The feasibility of autologous hematopoietic stem cell transplantation to improve pregnancy rates in patients with poor ovarian reserve has also been investigated with reported success rates in limited number of recent studies.

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Sp06

PRINCIPLES OF TRANSFUSION IN CHILDREN WITH CANCER

Dilek Gürlek Gökçebay

Transfusion therapy has an important role for pediatric cancer patients. A multicenter retrospective study of 4766 children with cancer demonstrated that 39.3% of the patients were given a transfusion. Red blood cells (RBCs) and platelets were the most commonly transfused components. Patients between 1 to <6 years of age were most likely to be transfused and HSCT, acute myeloid leukemia, and aplastic anemia were most often associated with transfusion.

Anemia occurs due to the suppression or dysfunction of erythropoiesis secondary to the underlying disease, as well as a consequence of bleeding in children with cancer. National audits of pediatric RBC transfusions in the United Kingdom have reported that more than half of pediatric transfusions were given to hematology/oncology patients. The balance between the tolerance to anemia and the need for transfusion may be different from other patients, because of underlying disease, the presence of comorbidities that influence the tolerance to anemia, and complications of multiple previous transfusions. In children with cancer undergoing hematopoietic stem cell transplantation (HSCT) who are at risk for critical illness and hemodynamically stable, suggested Hb value is 7 to 8 g/dL for the threshold of RBC transfusion. RBC transfusions are usually dosed as 10 to 15 mL/kg. However,the decision to transfuse should not be driven by the hemoglobin concentration, the patient’s clinical status should also be taken into consideration. Leukoreduction is one of the most common modifications to cellular blood components with universal leukoreduction being accepted increasingly as a standard. Cellular blood components including viable lymphocytes should also need to be irradiated in children with cancer. The gamma irradiation prevents T-lymphocytes from proliferating and reduces the risk of transfusion-associated

graft-versus-host disease (TA-GVHD), in patients with significant immunosuppression due to chemotherapy (eg. purine analogs), immunomodulators, radiation, or HSCT patients.

Thrombocytopenia can occur in nearly all children with cancer during their disease course as a result of bone marrow infiltration, chemotherapy, or associated illness, such as sepsis or disseminated intravascular coagulopathy. Platelet transfusions are prescribed to prevent or treat bleeding (referred to as prophylactic or therapeutic transfusions, respectively). In critically ill children with an underlying oncologic diagnosis, 71% of the platelet transfusions were given prophylactically. American Society of Clinical Oncology recommmends for a prophylactic platelet transfusion threshold of 10×10^9/L. However, a scarce data exists to platelet transfusion therapy in pediatric cancer patients with clinically relevant bleeding, fever, hyperleukocytosis, infection, or receiving anticoagulation. Dosing recommendation is 10 to 15 mL/kg of ideal body weight. Leucoreduction and irradiation are also recommended for platelet transfusions in pediatric cancer patients.

Fresh Frozen Plasma (FFP) is transfused to correct multiple coagulation factor deficiencies in patients with active bleeding (therapeutic transfusions) or to prevent bleeding before invasive procedures (prophylactic transfusions). Dosing recommendation is 10 to 20 mL/kg. Patients with cancer may be at risk for abnormalities of hemostasis due to tumor pathology (eg. AML M3) and evolution of the disease as well as treatment effect. Besides, FFP transfusion has significant risk that should be weighed against its perceived benefit.

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Sp07

AN APPROACH TO PAIN IN CHILDREN WITH CANCER

Yavuz Akçaboy

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or relating that associated with, actual or potential tissue damage." although this definition is made for adults, it also applies to children. pain is a very complex phenomenon and is modulated by many factors. It usually begins with a tissue injury, followed immediately by the activation of the neural pathway. but this physiological state cannot explain the experience of pain. the experience of pain depends on the person's interpretation.

About 15,000 children and adolescents are diagnosed with cancer in the United States every year, and 80% of them survive for a long time with their diseases. Almost all these children experience pain somewhere during their own cancer experience. This condition occurs either as a result of the disease itself, or as a side effect of treatment, or as a result of procedures related to their care. In the whole process of cancer, pain is the most common, severe and stressful symptom.

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Sp08

MEDICAL TREATMENT IN EWING SARCOMA

Roberto Luksch

Multidisciplinary treatment has improved the prognosis of Ewing sarcoma (ES) over the last decades, with the introduction of multi-agent chemotherapy and multidisciplinary patient management. This improvement was due from both the use of intensified systemic treatments and optimization of local treatments, using surgery and radiotherapy in different combinations and sequences.

Nowadays the treatment generally consists of induction chemotherapy, followed by surgery and/or local radiotherapy, and then maintenance chemotherapy.

Extended international collaboration has enabled prognostic groups to be better defined and risk-adapted treatment strategies to be tailored to patients.

The most remarkable steps along the way in which chemotherapy has improved the prognosis for ES are different: 1-The benefit of adding ifosfamide and etoposide (IE) to the vincristine, doxorubicin, and cyclophosphamide (VDC) combination for localized ES was demonstrated; this benefit was not demonstrated in patients with metastatic disease (Grier 2003). 2-The randomized EuroEwing99 R1 trial addressed the equivalence of ifosfamide and cyclophosphamide in localized disease: the conclusion was that cyclophosphamide might be able to replace ifosfamide in consolidation treatment of standard-risk ES (Le Deley 2016) 3-A randomized Childrens Oncology Group trial demonstrated that dose-intensifying chemotherapy by shortening the interval between treatments with the regimen VDC/IE (Vincristine+Doxorubicin+Cyclophosphamide, and Ifosfamide+Etoposide) led to a longer 5-year event-free survival in cases of localized disease. Compared with those assigned to the 3-week standard treatment interval, patients assigned to the 2-week treatment interval had a longer 5-year event-free survival (Womer 2012) . This result was corroborated by the EuroEWING Consortium Study 2012, where the compressed VDC/IE regimen was randomly compared with VIDE (vincristine, ifosfamide, doxorubicin, and etoposide), which was the backbone induction regimen of the EEC-99 trial (Brennan 2020). 4-The efficacy of a consolidation treatment with high-dose melphalan/busulfan (BuMel) + stem cell rescue was examined in prospective phase II non-randomized studies (Ferrari 2011), and in a large randomized study by the EuroEWING Consortium. For localized ES with a poor histological response to induction chemotherapy, there were signs of BuMel proving more effective than standard maintenance chemotherapy (Whelan 2018). Evidence of efficacy of BuMel in metastatic disease is limited to patients with pulmonary metastases, in which case its value is debatable, and has to be set against a significantly higher risk of severe acute and late side effects when compared with standard maintenance chemotherapy (Dirksen 2019).

There is an unmet medical need to improve prognosis of patients with synchronous metastatic disease or relapse. In the last decades, efficacy of new drugs was disappointing and no new drugs have been successfully introduced up to now in front

line treatment. Early clinical data suggest that strategies using multi-tyrosine kinase inhibitors (TKI) carrying anti-angiogenic activities are among the most active new drugs tested. Several TKI are currently being tested as single-agent in patients with relapse/refractory Ewing sarcoma with encouraging results in phase II trials, and may show efficacy (Attia 2017, Italiano 2020).

Given the complexity and rarity of Ewing sarcoma, it is essential for patients to be treated at selected reference institutions with specific expertise and multidisciplinary skills.

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