Publikationen Dr. med. Rolf Mahlberg

Beteiligung an Lehr- und Fachbüchern:

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2. Diagnostik und medikamentöse Therapie des Magenkarzinoms 2.Auflage Uni-Med Verlag 2016
3. Multiresistente Erreger Springer Verlag 2015
4. Hämatologie und Onkologie Thieme Verlag 2015
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Leitlinie „Lungenerkrankung bei Mukoviszidose“, Modul 1: Diagnostik und Therapie nach dem ersten Nachweis von Pseudomonas aeruginosa

Verantwortliche Autoren: F.M. Müller[a], J. Bend[o], E.Rietschel[c],
Co-Autoren: M. Abele-Horn[e]; M. Ballmann[a]; J. Bargon[b]; I. Baumann[i]; W. Bremer[d], R. Bruns[j], F. Brunsmann[p], R. Fischer[b]; C. Geidel[f], H. Hebestreit[c]; T. O. Hirche[b]; M. Hogardt[e], I. Huttegger[g], S. Illing[a], A. Koitschev[i]; M. Kohlhäufl[h], **R. Mahlberg[k]**; J. Mainz[a], A. Möller[f], S. Pfeiffer-Auler[d]; M. Puderbach[m], J. Riedler[g]; B. Schulte-Hubbert[l]; C. Schwarz[b], L. Sedlacek[e], H. Sitter, Ch. Smaczny[b], D. Staab[a]; B. Tümmler[a], R.-P. Vonberg[e]; T.O.F. Wagner[b]; J. Zerlik[n]

Mitgetragen durch

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T. Rabenstein, P. Reichardt, K. Ridwelski, C. Röcken, I. Roetzer, P. Rohr,W. Schepp, P. M. Schlag, R. M. Schmid, H. Schmidberger,
W.-H. Schmiegel, H.-J. Schmoll, G. Schuch, C. Schuhmacher, K. Schütte, W. Schwenk, M. Selgrad, A. Sendler, J. Seraphin, T. Seufferlein,
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1. Gastric Cancer. 2016 Jun 2. [Epub ahead of print]

Phase I study of orally administered S-1 in combination with epirubicin and oxaliplatin in patients with advanced solid tumors and chemotherapy-naïve advanced or metastatic esophagogastric cancer.

Moehler M(1), Mahlberg R(2), Heinemann V(3), Obermannová R(4), Kubala E(5), Melichar B(6), Weinmann A(7), Scigalla P(8), Tesařová M(9), Janda P(9), Hédouin-Biville F(10), Mansoor W(11).

Author information:
(1)I. Medizinische Klinik und Poliklinik, University Medical Center, Johannes Gutenberg-University Mainz, Langenbeckstraße 1, 55131, Mainz, Germany. markus.moehler@unimedizin-mainz.de. (2)Mutterhaus Der Borromaerinnen, Trier, Germany. (3)Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany. (4)Clinic of Comprehensive Cancer Care, MOU, Brno, Czech Republic. (5)Faculty Hospital Hradec Králové, Hradec Králové, Czech Republic. (6)Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic. (7)I. Medizinische Klinik und Poliklinik, University Medical Center,

Johannes Gutenberg-University Mainz, Langenbeckstraße 1, 55131, Mainz, Germany. (8)Pharmaceutical Research Consulting, Berlin, Germany. (9)Prague Clinical Services, Prague, Czech Republic. (10)Nordic Group, Paris, France. (11)The Christie Hospital NHS Foundation Trust, Manchester, UK.

BACKGROUND: This phase I study investigated the safety and the maximum tolerated dose (MTD) of the oral fluoropyrimidine S-1 when combined with epirubicin and oxaliplatin (EOS).
METHODS: Patients aged ≥18 years with advanced or metastatic solid tumors were enrolled in a 3 + 3 design with S-1 dose escalation (two planned cohorts) performed according to the occurrence of dose-limiting toxicity (DLT). On day 1 of each 21-day cycle, patients received epirubicin 50 mg/m(2) followed by oxaliplatin 130 mg/m(2) (maximum 8 cycles) and then S-1 [20 mg/m(2) (cohort 1) or 25 mg/m(2) (cohort 2), twice daily]: first dose, evening of day 1; subsequent administration on days 2-14, twice daily; last dose, morning of day 15 (unlimited number of S-1 cycles). After protocol amendment, enrollment in a third cohort was restricted to patients with chemotherapy-naïve advanced or metastatic esophagogastric cancer.
RESULTS: DLT was reported for two of the five patients in cohort 2, defining 20 mg/m(2) twice daily as the MTD of S-1 combined with epirubicin and oxaliplatin in heavily pretreated patients. Thirteen patients with chemotherapy-naïve advanced or metastatic esophagogastric cancer were subsequently enrolled and treated at an S-1 dose level of 25 mg/m(2) twice daily; no DLTs were reported; median overall survival was 13.1 months. Of the 11 evaluable patients, three (27 %) had partial responses and seven (64 %) had stable disease. The safety profile was in line with expectations.
CONCLUSIONS: The promising activity of EOS (S-1 dose level, 25 mg/m(2) twice daily) and acceptable safety profile support further clinical development of this combination for the first-line treatment of patients with advanced or metastatic esophagogastric cancer.

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2. Leukemia. 2016 Jun;30(6):1255-62. doi: 10.1038/leu.2016.20. Epub 2016 Feb 9.

Secondary malignancies in chronic myeloid leukemia patients after imatinib-based treatment: long-term observation in CML Study IV.

Miranda MB(1), Lauseker M(2), Kraus MP(1), Proetel U(1), Hanfstein B(1), Fabarius A(1), Baerlocher GM(3), Heim D(4), Hossfeld DK(5), Kolb HJ(6), Krause SW(7), Nerl C(8), Brümmendorf TH(9), Verbeek W(10), Fauser AA(11), Prümmer O(12), Neben K(13), Hess U(14), Mahlberg R(15), Plöger C(16), Flasshove M(17), Rendenbach B(18), Hofmann WK(1), Müller MC(1), Pfirrmann M(2), Hochhaus A(19), Hasford J(2), Hehlmann R(1), Saußele S(1).

Author information:
(1)III. Medizinische Klinik, Universitätsmedizin, Medizinische Fakultät Mannheim der Universität Heidelberg, Mannheim, Germany. (2)Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, Ludwig-Maximilians-Universität, München, Germany. (3)Universitätsklinik für Hämatologie und Hämatologisches Zentrallabor, Inselspital, Bern, Switzerland. (4)Klinik für Hämatologie, Universitätsspital, Basel, Switzerland. (5)II. Medizinische Klinik, Universitätsklinikum Eppendorf, Hamburg, Germany. (6)Medizinische Klinik und Poliklinik III, Klinikum der Ludwig-Maximilians-Universität, München, Germany. (7)Medizinische Klinik 5, Universitätsklinikum, Erlangen, Germany. (8)Klinik für Hämatologie, Onkologie, Immunologie, Palliativmedizin, Infektiologie und Tropenmedizin, Klinikum Schwabing, München, Germany. (9)Medizinische Klinik IV, Uniklinik RWTH, Aachen Germany. (10)Zentrum für ambulante Hämatologie und Onkologie, Bonn, Germany.

(11)Klinik für Knochenmarktransplantation und Hämatologie/Onkologie, Klinikum, Idar-Oberstein, Germany. (12)Klinik für Hämatologie, Onkologie und Palliativmedizin, Klinikum, Kempten, Germany. (13)Medizinische Klinik 2, Klinikum Mittelbaden, Standort Balg, Baden-Baden, Germany. (14)Klinik für Onkologie/Hämatologie, Kantonsspital, St Gallen, Switzerland. (15)Innere Medizin 1, Klinikum Mutterhaus der Borromäerinnen, Trier, Germany. (16)Mannheimer Onkologie Praxis, Mannheim, Germany. (17)Medizinische Klinik III, Krankenhaus, Düren, Germany. (18)Praxis für Innere Medizin, Nephrologie, Hämatologie und Onkologie, Trier, Germany. (19)Klinik für Innere Medizin II, Universitätsklinikum, Jena, Germany.

Treatment of chronic myeloid leukemia (CML) has been profoundly improved by the introduction of tyrosine kinase inhibitors (TKIs). Long-term survival with imatinib is excellent with a 8-year survival rate of ~88%. Long-term toxicity of TKI treatment, especially carcinogenicity, has become a concern. We analyzed data of the CML study IV for the development of secondary malignancies. In total, 67 secondary malignancies were found in 64 of 1525 CML patients in chronic phase treated with TKI (n=61) and interferon-α only (n=3). The most common malignancies (n⩾4) were prostate, colorectal and lung cancer, non-Hodgkin's lymphoma (NHL), malignant melanoma, non-melanoma skin tumors and breast cancer. The standardized incidence ratio (SIR) for all malignancies excluding non-melanoma skin tumors was 0.88 (95% confidence interval (0.63-1.20)) for men and 1.06 (95% CI 0.69-1.55) for women. SIRs were between 0.49 (95% CI 0.13-1.34) for colorectal cancer in men and 4.29 (95% CI 1.09-11.66) for NHL in women. The SIR for NHL was significantly increased for men and women. An increase in the incidence of secondary malignancies could not be ascertained. The increased SIR for NHL has to be considered and long-term follow-up of CML patients is warranted, as the rate of secondary malignancies may increase over time.

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3. Lancet. 2015 Apr 11;385(9976):1418-27. doi: 10.1016/S0140-6736(14)61469-0. Epub 2014 Dec 22.

Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial.

Behringer K(1), Goergen H(1), Hitz F(2), Zijlstra JM(3), Greil R(4), Markova J(5), Sasse S(1), Fuchs M(1), Topp MS(6), Soekler M(7), Mathas S(8), Meissner J(9), Wilhelm M(10), Koch P(11), Lindemann HW(12), Schalk E(13), Semrau R(14), Kriz J(11), Vieler T(15), Bentz M(16), Lange E(17), Mahlberg R(18), Hassler A(19), Vogelhuber M(20), Hahn D(21), Mezger J(22), Krause SW(23), Skoetz N(24), Böll B(1), von Tresckow B(1), Diehl V(1), Hallek M(25), Borchmann P(1), Stein H(26), Eich H(11), Engert A(27); German Hodgkin Study Group; Swiss Group for Clinical Cancer Research; Arbeitsgemeinschaft Medikamentöse Tumortherapie.

Author information:
(1)German Hodgkin Study Group (GHSG), Department of Internal Medicine 1, University Hospital of Cologne, Cologne, Germany. (2)Cantonal Hospital of St Gallen, St Gallen, Switzerland and SAKK Swiss Group for Clinical Cancer Research, Bern, Switzerland. (3)VU University Medical Center, Amsterdam, Netherlands. (4)Third Medical Department, Paracelcus Medical University, Salzburg, Austria. (5)University Hospital Kralovske Vinohrady, Third Faculty of Medicine, Charles University, Prague, Czech Republic. (6)University Hospital Würzburg, Würzburg, Germany. (7)University of Tübingen, Tübingen, Germany. (8)Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany. (9)University of Heidelberg, Heidelberg, Germany. (10)Klinikum Nürnberg,

Nürnberg, Germany. (11)University Hospital Münster, Münster, Germany. (12)Katholisches Krankenhaus, Hagen, Germany. (13)Department of Haematology and Oncology, Medical Centre, Otto-von-Guericke University Magdeburg, Magdeburg, Germany. (14)Department of Radiation Oncology, University Hospital of Cologne, Cologne, Germany. (15)Medizinische Klinik, Universitätsklinik Schleswig-Holstein, Kiel, Germany. (16)Medizinische Klinik, Städtisches Klinikum Karlsruhe, Germany. (17)Medizinische Klinik, Hämatologie/Onkologie, Evangelisches Krankenhaus, Hamm, Germany. (18)Medizinische Klinik, Krankenanstalt Mutterhaus d. Borromäerinnen, Trier, Germany. (19)Zentrum für Innere Medizin, Hämatologie/Onkologie, Charité Campus Mitte, Berlin, Germany. (20)Medizinische Klinik, Universitätsklinik Regensburg, Regensburg, Germany. (21)Klinik für Onkologie, Katharinenhospital, Stuttgart, Germany. (22)Medizinische Klinik-Hämatologie, Onkologie, Immunologie, Palliativmedizin, St. Vincentius-Kliniken gAG, Karlsruhe, Germany. (23)Department of Internal Medicine 5, Haematology/Oncology, University of Erlangen, Germany. (24)Cochrane Haematological Malignancies Group, Department of Internal Medicine 1, University Hospital of Cologne, Cologne, Germany. (25)Department of Internal Medicine 1, University Hospital of Cologne, Cologne, Germany. (26)Berlin Reference Center for Lymphoma and Haematopathology, Berlin, Germany. (27)German Hodgkin Study Group (GHSG), Department of Internal Medicine 1, University Hospital of Cologne, Cologne, Germany. Electronic address: a.engert@uni-koeln.de.

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BACKGROUND: The role of bleomycin and dacarbazine in the ABVD regimen (ie, doxorubicin, bleomycin, vinblastine, and dacarbazine) has been questioned, especially for treatment of early-stage favourable Hodgkin's lymphoma, because of the drugs' toxicity. We aimed to investigate whether omission of either bleomycin or dacarbazine, or both, from ABVD reduced the efficacy of this regimen in treatment of Hodgkin's lymphoma.
METHODS: In this open-label, randomised, multicentre trial (HD13) we compared two cycles of ABVD with two cycles of the reduced-intensity regimen variants ABV (doxorubicin, bleomycin, and vinblastine), AVD (doxorubicin, vinblastine, and dacarbazine), and AV (doxorubicin and vinblastine), in patients with newly diagnosed, histologically proven, classic or nodular, lymphocyte predominant Hodgkin's lymphoma. In each treatment group, 30 Gy involved-field radiotherapy (IFRT) was given after both cycles of chemotherapy were completed. From Jan 28, 2003, patients were centrally randomly assigned (1:1:1:1) with a minimisation method to the four groups. Because of high event rates, assignment to the AV and ABV groups stopped early, on Sept 30, 2005, and Feb 10, 2006; assignment to ABVD and AVD continued (1:1) until Sept 30, 2009. Our primary objective was to show non-inferiority of the experimental variants compared with ABVD in terms of freedom from treatment failure (FFTF), by excluding a difference of 6% after 5 years corresponding to a hazard ratio (HR) of 1.72, via a 95% CI. Analyses reported here include qualified patients only, and between-group comparisons include only patients recruited during the same period. The trial was registered, number ISRCTN63474366.
FINDINGS: Of 1502 qualified patients, 566, 198, 571, and 167 were randomly assigned to receive ABVD, ABV, AVD, or AV, respectively. 5 year FFTF was 93.1%, 81.4%, 89.2%, and 77.1% with ABVD, ABV, AVD, and AV, respectively. Compared with ABVD, inferiority of the dacarbazine-deleted variants was detected with 5 year differences of -11.5% (95% CI -18.3 to -4.7; HR 2.06 [1.21 to 3.52]) for ABV and -15.2% (-23.0 to -7.4; HR 2.57 [1.51 to 4.40]) for AV. Non-inferiority of AVD compared with ABVD could also not be detected (5 year difference -3.9%, -7.7 to -0·1; HR 1.50, 1.00 to 2.26). 178 (33%) of 544 patients given ABVD had WHO grade III or IV toxicity, compared with 53 (28%) of 187 given ABV, 142 (26%) of 539 given AVD, and 40 (26%) of 151 given AV. Leucopenia was the most common event, and highest in the groups given bleomycin.

INTERPRETATION: Dacarbazine cannot be omitted from ABVD without a substantial loss of efficacy. With respect to our predefined non-inferiority margin, bleomycin cannot be safely omitted either, and the standard of care for patients with early-stage favourable Hodgkin's lymphoma should remain ABVD followed by IFRT.
FUNDING: Deutsche Krebshilfe and Swiss State Secretariat for Education and Research.

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4. Blood. 2014 Jul 31;124(5):720-8. doi: 10.1182/blood-2013-10-535021. Epub 2014 Jun 17.

The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas.

Murawski N(1), Held G(1), Ziepert M(2), Kempf B(3), Viardot A(4), Hänel M(5), Witzens-Harig M(6), Mahlberg R(7), Rübe C(8), Fleckenstein J(8), Zwick C(1), Glass B(9), Schmitz N(9), Zeynalova S(2), Pfreundschuh M(1).

Author information:
(1)Klinik Innere Medizin I, Saarland University Medical School, Hamburg, Germany; (2)Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, Leipzig, Germany; (3)Klinikum Landshut, Landshut, Germany; (4)Universitätsklinikum Ulm, Ulm, Germany; (5)Klinikum Chemnitz, Chemnitz, Germany; (6)Medizinische Klinik V, Heidelberg University, Heidelberg, Germany; (7)Klinikum Mutterhaus der Borromäerinnen, Trier, Trier, Germany; (8)Klinik für Strahlentherapie, Saarland University Medical School, Hamburg, Germany; and. (9)Asklepios-Klinik St. Georg, Hamburg, Germany.

To define the role of radiotherapy and intrathecal prophylaxis in extralymphatic craniofacial involvement (ECFI) of aggressive B-cell lymphoma, we analyzed 11 consecutive German High-Grade Non-Hodgkin Lymphoma Study Group trials. ECFI occurred in 290/4155 (7.0%) patients (orbita, 31; paranasal sinuses, 93; main nasal cavity, 38; tongue, 27; remaining oral cavity, 99; salivary glands, 54). In a multivariable analysis adjusted for International Prognostic Index rituximab improved event-free and overall survival both in patients with and without ECFI. Three-year event-free (79% vs 79%; P = .842) and overall survival (86% vs 88%; P = .351) rates were similar in 145 patients receiving and 57 not receiving radiotherapy. Without rituximab, the 2-year cumulative rate of central nervous system (CNS) disease was increased in 205 ECFI patients compared with 2586 non-ECFI patients (4.2% vs 2.8%; P = .038), whereas this was not observed with rituximab (1.6% in 83 ECFI vs 3.4% in 1252 non-ECFI patients; P = .682). In 88 ECFI patients who received intrathecal prophylaxis with methotrexate, the 2-year rate of CNS disease was 4.2% compared with 2.3% in 191 patients who did not (P = .981). In conclusion, rituximab eliminates the increased risk for CNS disease in patients with ECFI. This retrospective analysis does not support intrathecal prophylaxis or radiotherapy to ECFI patients in complete remission/unconfirmed complete remission. These findings should be confirmed in a prospective study.

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5. Blood. 2013 Jul 4;122(1):83-92. doi: 10.1182/blood-2012-10-461749. Epub 2013 May

8.

The level of residual disease based on mutant NPM1 is an independent prognostic factor for relapse and survival in AML.

Shayegi N(1), Kramer M, Bornhäuser M, Schaich M, Schetelig J, Platzbecker U, Röllig C, Heiderich C, Landt O, Ehninger G, Thiede C; Study Alliance Leukemia (SAL).

Collaborators: Schulz-Abelius A, Friedrichsen K, Repp R, Helm G, Kiani A, Krost A, Thiel E, Baldus CD, Possinger K, Kühnhardt D, Görner M, Probst S, Weissinger F, Krümpelmann U, Pflüger KH, Diekmann C, Mayer J, Protivankova M, Hänel M, Herbst R, Pielken HJ, Hindahl H, Ehninger G, Schaich M, Mackensen A, Krause S, Geißler M, Bauer J, Serve H, Brandts C, Kiehl M, Stein W, Höffkes HG, Ranze O, Schmitz N, Stuhlmann R, Schmidt H, Buhrmann K, Dürk HA, Metzner D, Ho AD, Krämer A, Kaiser U, Bartholomäus A, Fauser AA, Basara N, Link H, Mahlmann S, Wolf M, Ritter B, Mantovani-Löffler L, Kürschner D, Neuhaus T, Hoffmann C, Fetscher S, Schmielau J, Lehnert H, Brüggemann S, Neubauer A, Sohlbach K, Schleyer E, Griesshammer M, Tischler HJ, Lutz L, Hentrich M, Berdel WE, Müller-Tidow C, Wandt H, Schäfer-Eckart K, Jakob A, Dresel I, Gaska T, Niemeyer E, Kozák T, Vydra J, Reichle A, Holler E, Heits F, Meinhardt A, Geer T, Hrusovsky I, Kanzler S, Reinel HH, Heidemann E, Kaesberger J, Aulitzky WE, Leimer L, Clemens MR, Mahlberg R, Frickhofen N, Fuhr HG, Einsele H, Goebeler ME, Sandmann M, Becker G.

Mutations of the NPM1 gene (NPM1mut) are among the most common genetic alterations in acute myeloid leukemia and are suitable for minimal residual disease detection. We retrospectively investigated the prognostic impact of NPM1mut-based minimal residual disease detection from bone marrow for development of relapse by using a newly developed real-time polymerase chain reaction based on locked nucleic acid-containing primers in 174 patients, 155 of whom were treated within prospective protocols. The prognostic value of 5 cutoff values after completion of treatment or after allogeneic transplantation was studied by using cause-specific hazard models. Subsequent validation using cross-validated partial likelihood analysis revealed that an increase of more than 1% NPM1mut/ABL1 was most prognostic for relapse after chemotherapy, whereas an increase of more than 10% NPM1mut/ABL1 was most prognostic for relapse after allogeneic transplantation. Univariate and multivariate analysis of disease-free survival and overall survival revealed a significantly worse outcome in patients with >1% NPM1mut/ABL1 and >10% NPM1mut/ABL1, respectively, which remained significant after adjustment for FLT3-internal tandem duplication status. Our results in a large data set define and optimize cutoff values for early diagnosis of molecular relapse. These results may be especially important for defining triggers for early therapeutic intervention.

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6. Lancet. 2013 Apr 6;381(9873):1203-10. doi: 10.1016/S0140-6736(12)61763-2. Epub 2013 Feb 20.

Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial.

Rummel MJ(1), Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, Ballo H, Stauch M, Roller F, Barth J, Hoelzer D, Hinke A, Brugger W; Study group indolent Lymphomas (StiL).

Collaborators: Rummel M, Kaiser U, Niederle N, Link H, Brugger W, Barth J,

Welslau M, Banat A, Hinke A, Knauf W, Kofahl-Krause D, Weidmann E, Klein M, Baldus M, Sandherr M, Aulmann C, Schlimok G, Baldus M, Böck HP, Balló H, Balser C, Weidenbach F, Behringer D, Krüger S, Mitrou PS, Bojko P, Abenhardt W, Breuer F, Brudler O, Brugger W, Burchardt A, Blau W, Banat A, Chow K, Cordes HJ, Clemens M, Mahlberg R, Dürk H, Eckart M, Eggert J, Fiechtner H, Fuxius S, Görner M, Just M, Schäfer E, Graubner M, Günther G, Hahn L, Hecker R, Heil G, Herrmann O, Hochdörfer S, Hoffmann T, Hünermund K, Immenschuh P, Burk M, Josten K, Kaiser U, Heide T, Katz F, Klein S, Knauf W, Tesch H, Kobbe G, Zohren F, Haas R, Koch M, Rauh J, Köchling G, Kofahl-Krause D, Ganser A, Kojouharoff G, Dingeldey G, Koniczek S, Link H, Kirsch J, Losem C, Maschmeyer G, Rothmann F, Matzdorff A, Mittermüller J, Müller S, Hahn M, Müller L, Müller-Hagen S, Neise M, Schalk K, Neuhaus T, Hens K, Niederle N, Heider A, Kloster G, Nowak H, Prümmer O, Reeb M, Hansen R, Rohrberg R, Hurtz HJ, Fritze D, Rost A, Brecht A, Kayser R, Bernhard H, Sandherr M, Perker M, Schauer M, Schlag R, Schliesser G, Käbisch A, Weber C, Schmidt UM, Schmidt-Wolf I, Brossart P, Schneider J, Schröder J, Schroeder M, Schütte HJ, Artmann KD, Schwaner I, Seipelt G, Koch U, Selbach J, Anhuf J, Söling U, Stauch M, Thiel E, Hofmann WK, Fischer L, Tischbirek K, von Grünhagen U, Wagner H, Wilke J, Wattad M, Reimer P, Weide R, Heymanns J, Weidmann E, Jäger E, Weiss J, Welslau M, Klausmann M, Wittmann G, Zimber J.

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Lancet. 2013 Apr 6;381(9873):1163-5.
Lancet. 2013 Sep 28;382(9898):1093-4.
Lancet. 2013 Sep 28;382(9898):1094-5.
Lancet. 2013 Sep 28;382(9898):1094.
Nat Rev Clin Oncol. 2013 May;10(5):251-2.

BACKGROUND: Rituximab plus chemotherapy, most often CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), is the first-line standard of care for patients with advanced indolent lymphoma, and for elderly patients with mantle-cell lymphoma. Bendamustine plus rituximab is effective for relapsed or refractory disease. We compared bendamustine plus rituximab with CHOP plus rituximab (R-CHOP) as first-line treatment for patients with indolent and mantle-cell lymphomas.
METHODS: We did a prospective, multicentre, randomised, open-label, non-inferiority trial at 81 centres in Germany between Sept 1, 2003, and Aug 31, 2008. Patients aged 18 years or older with a WHO performance status of 2 or less were eligible if they had newly diagnosed stage III or IV indolent or mantle-cell lymphoma. Patients were stratified by histological lymphoma subtype, then randomly assigned according to a prespecified randomisation list to receive either intravenous bendamustine (90 mg/m(2) on days 1 and 2 of a 4-week cycle) or CHOP (cycles every 3 weeks of cyclophosphamide 750 mg/m(2), doxorubicin 50 mg/m(2), and vincristine 1.4 mg/m(2) on day 1, and prednisone 100 mg/day for 5 days) for a maximum of six cycles. Patients in both groups received rituximab 375 mg/m(2) on day 1 of each cycle. Patients and treating physicians were not masked to treatment allocation. The primary endpoint was progression-free survival, with a non-inferiority margin of 10%. Analysis was per protocol. This study is registered with ClinicalTrials.gov, number NCT00991211, and the Federal Institute for Drugs and Medical Devices of Germany, BfArM 4021335.
FINDINGS: 274 patients were assigned to bendamustine plus rituximab (261 assessed) and 275 to R-CHOP (253 assessed). At median follow-up of 45 months (IQR 25-57), median progression-free survival was significantly longer in the bendamustine plus rituximab group than in the R-CHOP group (69.5 months [26.1 to not yet reached] vs 31.2 months [15.2-65.7]; hazard ratio 0.58, 95% CI 0.44-0.74; p<0.0001). Bendamustine plus rituximab was better tolerated than R-CHOP, with lower rates of alopecia (0 patients vs 245 (100%) of 245 patients who recieved ≥3 cycles; p<0.0001), haematological toxicity (77 [30%] vs 173 [68%]; p<0.0001), infections (96 [37%] vs 127 [50%]); p=0.0025), peripheral neuropathy (18 [7%] vs

73 [29%]; p<0.0001), and stomatitis (16 [6%] vs 47 [19%]; p<0.0001). Erythematous skin reactions were more common in patients in the bendamustine plus rituximab group than in those in the R-CHOP group (42 [16%] vs 23 [9%]; p=0.024). INTERPRETATION: In patients with previously untreated indolent lymphoma, bendamustine plus rituximab can be considered as a preferred first-line treatment approach to R-CHOP because of increased progression-free survival and fewer toxic effects.
FUNDING: Roche Pharma AG, Ribosepharm/Mundipharma GmbH.

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7. Eur J Clin Microbiol Infect Dis. 2013 May;32(5):679-89. doi: 10.1007/s10096-012-1794-4. Epub 2012 Dec 28.

Immediate versus deferred empirical antifungal (IDEA) therapy in high-risk patients with febrile neutropenia: a randomized, double-blind, placebo-controlled, multicenter study.

Maschmeyer G(1), Heinz WJ, Hertenstein B, Horst HA, Requadt C, Wagner T, Cornely OA, Löffler J, Ruhnke M; IDEA study investigators.

Collaborators: Aulitzky WE, Bertz H, Binder C, Buchholz S, Fauser AA, Hänel M, Heit W, Hoffmann M, Karthaus M, Keller U, Kiehl MG, Ludwig WD, Mahlberg R, Neuburger S, Niederwieser D, Pfreundschuh M, Schlimok G, Schmitz N, Schuler US, Carus CG, Schwerdtfeger R, Tagizadeh K, Thiel E, Ullmann AJ, Zander A.

Author information:
(1)Klinikum Ernst von Bergmann, Charlottenstrasse 72, 14467 Potsdam, Germany. gmaschmeyer@klinikumevb.de

Empirical antifungal therapy is widely used in high-risk neutropenic hematology patients with fever persisting for more than 4 days. This clinical trial assessed whether immediate empirical therapy with voriconazole could lower the rates of invasive fungal infections (IFIs) compared with this approach. In a double-blind, placebo-controlled, multicenter study, patients with acute leukemia undergoing chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT) recipients were randomized to broad-spectrum antibacterial therapy plus voriconazole (immediate) or placebo (deferred) after the onset of neutropenic fever. If fever persisted for 96 h, patients were switched to open-label intravenous voriconazole; oral treatment was permitted after 96 h. The primary endpoint was the rate of proven/probable IFIs between Days 2 and 28 after fever onset in the modified intent-to-treat (mITT) complete-case population. One hundred and forty-seven patients were randomized to immediate (n = 81) or deferred (n = 66) voriconazole. In the mITT population, six patients in the immediate group and nine in the deferred group developed proven/probable IFI between Days 2 and 28 (p = 0.258). The safety profiles were similar in both groups. While immediate empirical therapy with voriconazole appears to be safe in febrile neutropenic high-risk patients, it was not associated with a significant reduction in IFIs compared with therapy deferred for 96 h after fever onset.

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8. Eur J Cancer. 2013 Mar;49(4):835-42. doi: 10.1016/j.ejca.2012.09.025. Epub 2012 Oct 11.

The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+).

Al-Batran SE(1), Pauligk C, Homann N, Hartmann JT, Moehler M, Probst S, Rethwisch V, Stoehlmacher-Williams J, Prasnikar N, Hollerbach S, Bokemeyer C, Mahlberg R, Hofheinz RD, Luley K, Kullmann F, Jäger E.

Author information:
(1)Institut für Klinische Forschung und Klinik für Onkologie und Hämatologie am Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt am Main, Germany. albatran@aol.com

BACKGROUND: We evaluated the feasibility and tolerability of triple- versus double-drug chemotherapy in elderly patients with oesophagogastric cancer.
METHODS: Patients aged 65 years or older with locally advanced or metastatic oesophagogastric cancer were stratified and randomised to infusional 5-FU, leucovorin and oxaliplatin without (FLO) or with docetaxel 50 mg/m(2) (FLOT) every 2 weeks. The study is registered at ClinicalTrials.gov, identifier NCT00737373.
FINDINGS: One hundred and forty three (FLO, 71; FLOT, 72) patients with a median age of 70 years were enrolled. The triple combination was associated with more treatment-related National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3/4 adverse events (FLOT, 81.9%; FLO, 38.6%; P<.001) and more patients experiencing a ≥10-points deterioration of European Organization for Research and Treatment of Cancer Quality of Life (EORTC QoL) global health status scores (FLOT, 47.5%; FLO 20.5%; p=.011). The triple combination was associated with more alopecia (P<.001), neutropenia (P<.001), leukopenia (P<.001), diarrhoea (P=.006) and nausea (P=.029).). No differences were observed in treatment duration and discontinuation due to toxicity, cumulative doses or toxic deaths between arms. The triple combination improved response rates and progression-free survival in the locally advanced subgroup and in the subgroup of patients aged between 65 and 70 years but not in the metastatic group or in patients aged 70 years and older.
INTERPRETATION: The triple-drug chemotherapy was feasible in elderly patients with oesophagogastric cancer. However, toxicity was significantly increased and QoL deteriorated in a relevant proportion of patients.
FUNDING: The study was partially funded by Sanofi-Aventis.

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9. Blood. 2012 Aug 23;120(8):1691-702. Epub 2012 Apr 19.

SOCS1 cooperates with FLT3-ITD in the development of myeloproliferative disease by promoting the escape from external cytokine control.

Reddy PN(1), Sargin B, Choudhary C, Stein S, Grez M, Müller-Tidow C, Berdel WE, Serve H, Brandts CH; Study Alliance Leukemia (SAL).

Collaborators: Schulz-Abelius A, Friedrichsen K, Repp R, Helm G, Kiani A, Krost A, Thiel E, Baldus C, Possinger K, Kühnhardt D, Görner M, Probst S, Pflüger KH, Diekmann C, Mayer J, Protivankova M, Hänel M, Herbst R, Pielken HJ, Hindahl H, Ehninger G, Schaich M, Mackensen A, Krause S, Serve H, Brandts C, Kiehl M, Stein W, Höffkes HG, Ranze O, Schmitz N, Stuhlmann R, Schmidt H, Buhrmann K, Dürk HA, Metzner D, Ho A, Bellos F, Kaiser U, Bartholomäus A, Fauser AA, Basara N, Link H, Mahlmann S, Wolf M, Ritter B, Löffler LM, Kürschner D, Neuhaus T, Hoffmann C, Fetscher S, Schmielau J, Lehnert H, Brüggemann S, Neubauer A, Sohlbach K, Schleyer E, Griesshammer M, Tischler HJ, Lutz L, Hentrich M, Berdel W,

Müller-Tidow C, Wilhem M, Schäfer-Eckart K, Jakob A, Dresel I, Gaska T, Niemeyer E, Kozák T, Vydra J, Reichle A, Holler E, Heits F, Meinhardt A, Geer T, Hrusovsky I, Kanzler S, Reinel HH, Heidemann E, Kaesberger J, Aulitzky WE, Leimer L, Clemens MR, Mahlberg R, Frickhofen N, Fuhr HG, Sandmann M, Becker G, Einsele H, Goebeler ME.

Activating mutations in the receptor tyrosine kinase FLT3 are frequently found in acute myelogenous leukemia patients and confer poor clinical prognosis. It is unclear how leukemic blasts escape cytokine control that regulates normal hematopoiesis. We have recently demonstrated that FLT3-internal tandem duplication (ITD), when localized to the biosynthetic compartment, aberrantly activates STAT5. Here, we show that one of the target genes induced by STAT5 is suppressor of cytokine signaling (SOCS)1-a surprising finding for a known tumor suppressor. Although SOCS1 expression in murine bone marrow severely impaired cytokine-induced colony growth, it failed to inhibit FLT3-ITD-supported colony growth, indicating resistance of FLT3-ITD to SOCS1. In addition, SOCS1 coexpression did not affect FLT3-ITD-mediated signaling or proliferation. Importantly, SOCS1 coexpression inhibited interferon-α and interferon-γ signaling and protected FLT3-ITD hematopoietic cells from interferon-mediated growth inhibitory effects. In a murine bone marrow transplantation model, the coexpression of SOCS1 and FLT3-ITD significantly shortened the latency of a myeloproliferative disease compared with FLT3-ITD alone ($P < .01$). Mechanistically, SOCS proteins shield FLT3-ITD from external cytokine control, thereby promoting leukemogenesis. The data demonstrate that SOCS1 acts as a conditional oncogene, providing novel molecular insights into cytokine resistance in oncogenic transformation. Restoring cytokine control may provide a new way of therapeutic intervention.

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10. Lancet Oncol. 2012 Feb;13(2):207-14. doi: 10.1016/S1470-2045(11)70326-6. Epub 2011 Dec 22.

Prediction of post-remission survival in acute myeloid leukaemia: a post-hoc analysis of the AML96 trial.

Pfirrmann M(1), Ehninger G, Thiede C, Bornhäuser M, Kramer M, Röllig C, Hasford J, Schaich M; Study Alliance Leukaemia (SAL).

Collaborators: Dörken B, Huhn D, Knigge O, Rick O, Siegert W, Hesse-Amojo J, Kolloch R, Krümpelmann U, Pflüger K-, Wolff T, Heidtmann H-, Marquard F, Hänel M, Fiedler F, Herbst R, Gramatzki M, Helm G, Beelen D, Saal J-, Arland M, Finke J, Fasshauer E, Zander A, Schmitz N, Stuhlmann R, Schmidt H, Buhrmann K, Dürk H, Burk M, Ganser A, Ho A, Krämer A, Fauser A, Kaiser U, Bartholomäus A, Link H, Hagmann F-, Köchling G, Schalk K-, Fetscher S, Wagner T, Neubauer A, Bodenstein H, Tischler J, Kolb H-, Pohlmann H, Brack N, Wandt H, Schäfer-Eckart K, Seeber B, Hirsch F, Geer T, Heissmeyer H, Labenz J, Aulitzky W, Kaufmann M, Kaesberger J, Clemens M, Mahlberg R, Kanz L, Schwerdtfeger R, Engberding R, Winter R, Sandmann M, Einsele H, Rückle-Lanz H, Greiner L.

Author information:
(1)Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie-IBE, Ludwig-Maximilians-Universität, Munich, Germany.

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Lancet Oncol. 2012 Feb;13(2):121-3.

BACKGROUND: The optimum post-remission treatment (PRT) in acute myeloid leukaemia (AML) is still a matter of debate. Consolidation treatments include chemotherapy

with high-dose cytarabine, or allogeneic or autologous haemopoietic stem cell transplantation (HSCT). In a post-hoc analysis of the AML96 trial (NCT00180115), our aim was to differentiate groups of patients according to the treatments that would provide them optimum benefit.
METHODS: In the multicentre AML96 trial, 586 patients (aged 15-60 years) with AML--excluding those with t(8;21)--who were in complete remission after double induction treatment were consolidated with allogeneic HSCT, autologous HSCT, or chemotherapy containing high-dose cytarabine in a priority-based and risk-adapted manner. We assessed the association between potentially prognostic variables and overall survival after complete remission by use of a stratified Cox regression analysis. With the significant variables of the resulting model, we developed a PRT score in 452 patients with a complete dataset. This score was then validated by use of data from 407 patients from the AML2003 trial (NCT00180102).
FINDINGS: Age, percentage of CD34-positive blasts, FLT3-ITD mutant-to-wild-type ratio, cytogenetic risk, and de-novo or secondary AML were identified as independent prognostic factors, and included in the PRT score. The PRT score separated patients in AML96 into three groups: favourable (n=190; 3-year survival 68%, 95% CI 60-74), intermediate (n=198; 49%, 42-56), and unfavourable (n=64; 20%, 12-31). All pair-wise comparisons of two of three PRT score groups were significant in the log-rank test (p<0·0001). Similar results were noted when data from AML2003 were used: 3-year survival for the favourable group (n=265) was 69% (62-76), for the intermediate group (n=114) it was 61% (50-71), and for the unfavourable group (n=28) it was 46% (24-65). The overall comparison between the three risk groups resulted in significantly different survival probabilities (p=0·015). We also analysed response to treatment in AML96 in each of the PRT score groups. In the favourable group, patients given allogeneic HSCT (n=60) had higher survival probabilities (82%, 69-89) than did those given chemotherapy (n=56, 55%, 41-67; p=0·0012) or autologous HSCT (n=74, 66%, 54-76; p=0·044). In the intermediate PRT score group, patients given autologous HSCT (n=69) had the best survival probabilities (62%, 50-72) compared with those given chemotherapy (n=72, 41%, 30-52; p=0·0006) or allogeneic HSCT (n=57, 44%, 31-56; p=0·0045).
INTERPRETATION: The PRT score groups could help physicians to tailor treatment for patients with AML and our results lend support to the use of autologous HSCT in patients aged 60 years or younger with an intermediate PRT score.
FUNDING: Deutsche Krebshilfe.

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PMID: 22197676 [PubMed - indexed for MEDLINE]

11. Z Gastroenterol. 2011 Apr;49(4):461-531. doi: 10.1055/s-0031-1273201. Epub 2011 Apr 7.

[German S3-guideline "Diagnosis and treatment of esophagogastric cancer"].

[Article in German]

Moehler M, Al-Batran SE, Andus T, Anthuber M, Arends J, Arnold D, Aust D, Baier P, Baretton G, Bernhardt J, Boeing H, Böhle E, Bokemeyer C, Bornschein J, Budach W, Burmester E, Caca K, Diemer WA, Dietrich CF, Ebert M, Eickhoff A, Ell C, Fahlke J, Feussner H, Fietkau R, Fischbach W, Fleig W, Flentje M, Gabbert HE, Galle PR, Geissler M, Gockel I, Graeven U, Grenacher L, Gross S, Hartmann JT, Heike M, Heinemann V, Herbst B, Herrmann T, Höcht S, Hofheinz RD, Höfler H, Höhler T, Hölscher AH, Horneber M, Hübner J, Izbicki JR, Jakobs R, Jenssen C, Kanzler S, Keller M, Kiesslich R, Klautke G, Körber J, Krause BJ, Kuhn C, Kullmann F, Lang H, Link H, Lordick F, Ludwig K, Lutz M, Mahlberg R, Malfertheiner P, Merkel S, Messmann H, Meyer HJ, Mönig S, Piso P, Pistorius S, Porschen R, Rabenstein T, Reichardt P, Ridwelski K, Röcken C, Roetzer I, Rohr P, Schepp W, Schlag PM, Schmid RM, Schmidberger H, Schmiegel WH, Schmoll HJ, Schuch

G, Schuhmacher C, Schütte K, Schwenk W, Selgrad M, Sendler A, Seraphin J, Seufferlein T, Stahl M, Stein H, Stoll C, Stuschke M, Tannapfel A, Tholen R, Thuss-Patience P, Treml K, Vanhoefer U, Vieth M, Vogelsang H, Wagner D, Wedding U, Weimann A, Wilke H, Wittekind C; AWMF; AWMF.

Collaborators: Al-Batran SE, Thuss-Patience P, Horneber M, Körber J, Link H, Anthuber M, Hölscher A, Lang H, Meyer HJ, Grenacher L, Flentje M, Höcht S, Burmester E, Dietrich C, Jenssen C, Hoelscher A, Meyer HJ, Ludwig K, Pistorius S, Stein H, Arends J, Weimann A, Boeing H, Hegewisch-Becker S, Höhler T, Lordick F, Stahl M, Möhler M, Knabbe C, Wagener C, Bockisch A, Krause BJ, Baretton G, Gabbert HE, Höfler H, Röcken C, Ebert M, Fischbach W, Möhler M, Seufferlein T, Gebest HJ, Treml K, Diemer W, Fabian R, Rohr P, Lutz M, Messmann H, Schepp W, Körber J, Keller M, Gross S, Wittekind C, Böhle E, Tholen R, Budach W, Ebert M, Schmid RM, Junker U, Uberall M, Fischbach W, Malfertheiner P, Vieth M, Ebert M, Lordick F, Sendler A, Messmann H, Caca K, Hölscher A, Ludwig K, Meyer HJ, Mönig S, Schuhmacher C, Stahl M, Al-Batran SE, Möhler M, Wagner D, Arends J, Boehle E, Link H, Körber J, Hübner J, Keller M, Nothacker M, Möhler M.

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12. Leukemia. 2011 Mar;25(3):420-8. doi: 10.1038/leu.2010.279. Epub 2010 Dec 7.

Risk stratification using a new prognostic score for patients with secondary acute myeloid leukemia: results of the prospective AML96 trial.

Stölzel F(1), Pfirrmann M, Aulitzky WE, Kaufmann M, Bodenstein H, Bornhäuser M, Röllig C, Kramer M, Mohr B, Oelschlägel U, Schmitz N, Soucek S, Thiede C, Ehninger G, Schaich M; Study Alliance Leukemia.

Collaborators: Huhn D, Knigge O, Spaeth-Schwalbe E, Hesse-Amojo S, Rick O, Siegert W, Thiel E, Uharek L, Kolloch R, Kümpelmann U, Pflueger KH, Wolff T, Heidtmann HH, Marquard F, Hänel M, Fiedler F, Herbst R, Gramatzki M, Helm G, Saal JG, Hoeffkes HG, Arland M, Fasshauer E, Stuhlmann R, Schmidt H, Buhrmann K, Duerk H, Burk M, Ho AD, Mahlknecht U, Bartholomaeus A, Fauser AA, Link H, Hagmann FG, Koechling G, Schalk KP, Fetscher S, Wagner T, Neubauer A, Tischler J, Pohlmann H, Brack N, Wilhelm M, Wandt H, Schaefer-Eckart K, Seeber B, Hirsch F, Geer T, Heissmeyer H, Labenz J, Kaesberger J, Leimer L, Clemens MR, Mahlberg R, Schwerdtfeger R, Engberding R, Winter R, Sandmann M, Einsele H, Weissinger F, Rueckle-Lanz H.

Author information:
(1)Medizinische Klinik und Poliklinik I, University Hospital Carl Gustav Carus Dresden, Dresden, Germany. friedrich.stoelzel@uniklinikum-dresden.de

Patients with secondary acute myeloid leukemia (sAML) are generally thought to have a poor prognosis. As there are no prognostic risk stratification models for patients with sAML available, the aim of this study was to obtain a scoring system. Prognostic factors influencing overall survival (OS) and event-free survival (EFS) were analyzed in 305 sAML patients treated in the prospective AML96 trial. The obtained prognostic scoring system was then validated in an independent patient cohort included in the AML2003 and AML60+ trials. In addition to the known risk factors for AML, age and karyotype, we identified the absolute platelet count and the Nucleophosmin 1 mutational status at diagnosis as prognostic factors of sAML patients. A pronounced distribution of sAML patients into three score groups was achieved showing a 2-year OS/EFS of 52/44% for patients in the low-risk group, 21/12% in the intermediate-risk group and 7/3% in the high-risk group (both P<0.001). Validation of this scoring system in a second independent set of sAML patients revealed similar significantly different survival results. In conclusion, for the first time, a prognostic scoring system

is provided for sAML patients, allowing differential treatment strategies in the future.

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13. Lancet. 2010 Dec 11;376(9757):2000-8. doi: 10.1016/S0140-6736(10)62105-8. Epub 2010 Dec 3.

Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes.

Krug U(1), Röllig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, Thiede C, Kramer M, Braess J, Spiekermann K, Haferlach T, Haferlach C, Koschmieder S, Rohde C, Serve H, Wörmann B, Hiddemann W, Ehninger G, Berdel WE, Büchner T, Müller-Tidow C; German Acute Myeloid Leukaemia Cooperative Group; Study Alliance Leukemia Investigators.

Collaborators: Fuss H, Hennesser D, Potenberg J, Ludwig WD, Schöndube D, Späth-Schwalbe E, Hesse-Amojo S, Mayr A, Grüneisen A, Boewer C, Derwahl M, Englisch HJ, Rick O, Siegert W, Notter M, Uharek L, Thiel E, Dörken B, Arnold R, Huhn D, Knigge O, Kolloch R, Krümpelmann U, Weh AJ, Zumsprekel A, Teschendorf C, Stechstor M, Trenn G, Wörmann B, Pflüger KH, Wolff T, Hertenstein B, Thomssen H, Peyn A, Rasche H, Heidtmann HH, Marquard F, Hähnel M, Fiedler F, Herbst R, Hallek M, Staib P, Heike M, Niederste-Hollenberg A, Pielken H, Hindahl H, Röllig C, Schaich M, Thiede C, Kramer M, Ehninger G, Aul C, Giagounidis A, Lange W, Kuhlemann SE, Flasshove M, Karow J, Gramatzki M, Helm G, Fuchs R, Schlegel F, Saal JG, Serve H, Kiehl M, Höffkes HG, Arland M, Meckenstock G, Giagounidis A, Haase D, Trümper L, Griesinger F, Gropp C, Depenbusch R, Eimermacher H, Schütte W, Haak U, Fasshaür E, Schmitz N, Stuhlmann R, Braumann D, Schmidt H, Buhrmann K, Balleisen L, Schubert J, Dürk H, Burk M, Ho AD, Mahlknecht U, Lange JG, Schmitz-Hübner U, Bartholomäus A, Fauser A, Link H, Hagmann FG, Wolf M, Ritter B, Frieling T, Planker M, Köchling G, Hartmann F, Middeke H, Gründgens C, Constantin C, Schalk KP, Jost KA, Fetscher S, Schmielau J, Wagner T, Uppenkamp M, Hoffmann M, Hehlmann R, Lengfelder E, Neubauer A, Schwonzen M, Spangenberg H, Bodenstein H, Tischler J, Graeven D, Kohl D, Heuer T, Pohlmann H, Brack N, Nibler K, Fleckenstein D, Haferlach T, Haferlach C, Schnittger S, Kern W, Emmerich B, Dengler R, Schlag B, Hiddemann W, Braess J, Spiekermann K, Berdel WE, Büchner T, Kienast J, Mesters R, Müller-Tidow C, Krug U, Koschmieder S, Volpert S, Wieacker P, Sauerland MC, Heinecke A, Köpcke W, Wilhelm M, Wandt H, Schäfer-Eckart K, Hirsch F, Seeber B, Hartlapp J, Hegge T, Peceny R, Koch O, Innig G, Südhoff T, Wagner T, Maschmeyer G, Kreuser ED, Schenk M, Reichle A, Andreesen R, Huff H, Schönberger D, Geer T, Heissmeyer H, Labenz J, Gassmann W, Gaske T, Käsberger J, Aulitzky WE, Leimer L, Clemens MR, Mahlberg R, Frickhofen N, Fuhr HG, Schwerdtfeger R, Augener W, Engberding R, Winter R, Sandmann M, Einsele H, Weissinger F, Rückle-Lanz H, Brugger W, Papakonstantinou G, Kreibich U, Schott G, Sommer S, Zschille W.

Comment in
Lancet. 2010 Dec 11;376(9757):1967-8.

BACKGROUND: About 50% of patients (age ≥60 years) who have acute myeloid leukaemia and are otherwise medically healthy (ie, able to undergo intensive chemotherapy) achieve a complete remission (CR) after intensive chemotherapy, but with a substantially increased risk of early death (ED) compared with younger patients. We verified the association of standard clinical and laboratory variables with CR and ED and developed a web-based application for risk assessment of intensive chemotherapy in these patients.
METHODS: Multivariate regression analysis was used to develop risk scores with or

without knowledge of the cytogenetic and molecular risk profiles for a cohort of 1406 patients (aged ≥60 years) with acute myeloid leukaemia, but otherwise medically healthy, who were treated with two courses of intensive induction chemotherapy (tioguanine, standard-dose cytarabine, and daunorubicin followed by high-dose cytarabine and mitoxantrone; or with high-dose cytarabine and mitoxantrone in the first and second induction courses) in the German Acute Myeloid Leukaemia Cooperative Group 1999 study. Risk prediction was validated in an independent cohort of 801 patients (aged >60 years) with acute myeloid leukaemia who were given two courses of cytarabine and daunorubicin in the Acute Myeloid Leukaemia 1996 study.
FINDINGS: Body temperature, age, de-novo leukaemia versus leukaemia secondary to cytotoxic treatment or an antecedent haematological disease, haemoglobin, platelet count, fibrinogen, and serum concentration of lactate dehydrogenase were significantly associated with CR or ED. The probability of CR with knowledge of cytogenetic and molecular risk (score 1) was from 12% to 91%, and without knowledge (score 2) from 21% to 80%. The predicted risk of ED was from 6% to 69% for score 1 and from 7% to 63% for score 2. The predictive power of the risk scores was confirmed in the independent patient cohort (CR score 1, from 10% to 91%; CR score 2, from 16% to 80%; ED score 1, from 6% to 69%; and ED score 2, from 7% to 61%).
INTERPRETATION: The scores for acute myeloid leukaemia can be used to predict the probability of CR and the risk of ED in older patients with acute myeloid leukaemia, but otherwise medically healthy, for whom intensive induction chemotherapy is planned. This information can help physicians with difficult decisions for treatment of these patients.
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14. Blood. 2010 Aug 12;116(6):971-8. doi: 10.1182/blood-2010-01-267302. Epub 2010 May 4.

A novel prognostic model in elderly patients with acute myeloid leukemia: results of 909 patients entered into the prospective AML96 trial.

Röllig C(1), Thiede C, Gramatzki M, Aulitzky W, Bodenstein H, Bornhäuser M, Platzbecker U, Stuhlmann R, Schuler U, Soucek S, Kramer M, Mohr B, Oelschlaegel U, Stölzel F, von Bonin M, Wermke M, Wandt H, Ehninger G, Schaich M; Study Alliance Leukemia.

Collaborators: Huhn D, Knigge O, Späth-Schwalbe E, Hesse-Amojo S, Rick O, Siegert W, Thiel E, Uharek L, Kolloch R, Krümpelmann U, Pflüger KH, Wolff T, Heidtmann HH, Marquard F, Hähnel M, Fiedler F, Herbst R, Gramatzki M, Helm G, Saal JG, Höffkes HG, Arland M, Fasshaür E, Schmitz N, Stuhlmann R, Schmidt H, Buhrmann K, Dürk H, Burk M, Ho AD, Mahlknecht U, Bartholomäus A, Fauser AA, Link H, Hagmann FG, Köchling G, Schalk KP, Fetscher S, Wagner T, Neubaür A, Bodenstein H, Tischler J, Pohlmann H, Brack N, Wilhelm M, Wandt H, Schäfer-Eckart K, Seeber B, Hirsch F, Geer T, Heissmeyer H, Labenz J, Käsberger J, Aulitzky WE, Leimer L, Clemens MR, Mahlberg R, Schwerdtfeger R, Engberding R, Winter R, Sandmann M, Einsele H, Weissinger F, Rückle-Lanz H.

Author information:
(1)Medizinische Klinik und Poliklinik I, Universitätsklinikum Dresden, Fetscherstrasse 74, Dresden, Germany. christoph.roellig@uniklinikumdresden.de

We present an analysis of prognostic factors derived from a trial in patients with acute myeloid leukemia older than 60 years. The AML96 trial included 909

patients with a median age of 67 years (range, 61-87 years). Treatment included cytarabine-based induction therapy followed by 1 consolidation. The median follow-up time for all patients is 68 months (5.7 years). A total of 454 of all 909 patients reached a complete remission (50%). Five-year overall survival (OS) and disease-free survival were 9.7% and 14%, respectively. Multivariate analyses revealed that karyotype, age, NPM1 mutation status, white blood cell count, lactate dehydrogenase, and CD34 expression were of independent prognostic significance for OS. On the basis of the multivariate Cox model, an additive risk score was developed that allowed the subdivision of the largest group of patients with an intermediate-risk karyotype into 2 groups. We are, therefore, able to distinguish 4 prognostic groups: favorable risk, good intermediate risk, adverse intermediate risk, and high risk. The corresponding 3-year OS rates were 39.5%, 30%, 10.6%, and 3.3%, respectively. The risk model allows further stratification of patients with intermediate-risk karyotype into 2 prognostic groups with implications for the therapeutic strategy.

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PMID: 20442365 [PubMed - indexed for MEDLINE]

15. Blood. 2009 Nov 5;114(19):4197-208. doi: 10.1182/blood-2008-12-190934. Epub 2009 Sep 4.

E3 ligase-defective Cbl mutants lead to a generalized mastocytosis and myeloproliferative disease.

Bandi SR(1), Brandts C, Rensinghoff M, Grundler R, Tickenbrock L, Köhler G, Duyster J, Berdel WE, Müller-Tidow C, Serve H, Sargin B; Study Alliance Leukemias.

Collaborators: Aul C, Aulitzky WE, Bentz M, Berdel W, Cetkovsky P, Dörken B, Dührsen U, Dürfeld BM, Dürk HA, Ehninger G, Einsele H, Fauser AA, Fetscher S, Frickhofen N, Frühauf S, Gaska T, Geer T, Geissler M, Görner M, Griesshammer M, Hänel M, Heits F, Hentrich M, Ho A, Höffkes HG, Jakob A, Kaesberger J, Kaiser U, Kiehl M, Klein S, Kozák T, Krause S, Lanska M, Link H, Ludwig L, Mahlberg R, Löffler LM, Mayer J, Neubauer A, Neuhaus T, Pflüger KH, Pfreundschuh M, Pielken HJ, Possinger K, Reichele A, Reinel HH, Repp R, Sandmann M, Schleyer E, Schmidt H, Schmitz N, Schulz-Abelius A, Serve H, Thiel E, Wagner T, Wandt H, Wolf M.

Author information:
(1)Department of Medicine, Hematology and Oncology and the Interdisciplinary Center for Clinical Research, University Hospital Muenster, Muenster, Germany.

Somatic mutations of Kit have been found in leukemias and gastrointestinal stromal tumors. The proto-oncogene c-Cbl negatively regulates Kit and Flt3 by its E3 ligase activity and acts as a scaffold. We recently identified the first c-Cbl mutation in human disease in an acute myeloid leukemia patient, called Cbl-R420Q. Here we analyzed the role of Cbl mutants on Kit-mediated transformation. Coexpression of Cbl-R420Q or Cbl-70Z with Kit induced cytokine-independent proliferation, survival, and clonogenic growth. Primary murine bone marrow retrovirally transduced with c-Cbl mutants and transplanted into mice led to a generalized mastocytosis, a myeloproliferative disease, and myeloid leukemia. Overexpression of these Cbl mutants inhibited stem cell factor (SCF)-induced ubiquitination and internalization of Kit. Both Cbl mutants enhanced the basal activation of Akt and prolonged the ligand-dependent activation. Importantly, transformation was observed also with kinase-dead forms of Kit and Flt3 in the presence of Cbl-70Z, but not in the absence of Kit or Flt3, suggesting a mechanism dependent on receptor tyrosine kinases, but independent of their kinase activity. Instead, transformation depends on the Src family kinase Fyn, as c-Cbl coimmunoprecipitated with Fyn and inhibition abolished transformation. These findings may explain primary resistance to tyrosine kinase inhibitors targeted at

receptor tyrosine kinases.

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PMID: 19734451 [PubMed - indexed for MEDLINE]

16. Leukemia. 2009 Apr;23(4):656-63. doi: 10.1038/leu.2008.375. Epub 2009 Jan 8.

The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia.

Seifert H(1), Mohr B, Thiede C, Oelschlägel U, Schäkel U, Illmer T, Soucek S, Ehninger G, Schaich M; Study Alliance Leukemia (SAL).

Collaborators: Siegert W, Rick O, Thiel E, Späth-Schwalbe E, Hesse-Amojo S, Kolloch R, Krümpelmann U, Görner M, Probst S, Pflüger KH, Wolff T, Heidtmann H, Kalcki L, Hotz J, Marquard F, Hänel M, Herbst R, Ehninger G, Schaich M, Grammatzki M, Helm G, Saal JG, Höffkes HG, Arland M, Fasshauer E, Opitz B, Kuse R, Schmitz N, Stuhlmann R, Schmidt H, Buhrmann K, Dürk H, Bechtel B, Teschke R, Burk M, Ho A, Kaiser U, Bartholomäus A, Fauser AA, Zimber S, Link H, Hagmann FG, Mantovani L, Schalk KP, Fetscher S, Wagner T, Neubauer A, Bodenstein H, Tischler J, Hartenstein R, Brack N, Pohlmann H, Wilhelm W, Wandt H, Schäfer-Eckardt K, Dancygier H, Seeber B, Hirsch F, Dressel I, Heissmeyer H, Geer T, Jähde E, Labenz J, Aulitzky W, Leimer L, Heidemann E, Kaesberger J, Clemens MR, Mahlberg R, Schwerdtfeger R, Engberding R, Winter R, Wilms K, Rücke-Lanz H, Weissinger F, Sandmann M, Hellmann A.

Author information:
(1)Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus, Dresden, Germany.

Loss of p53 -- a tumor suppressor gene located on the short arm of chromosome 17 (band 17p13.1) -- was detected in 105 out of 2272 (5%) adult acute myeloid leukemia (AML) patients who took part in the Study Alliance Leukemia AML96 and AML2003 multi center trials. There were 85 patients with 17p (p53) deletion with multiple aberrations and 20 patients with a 17p (p53) deletion as single aberration or with only one additional chromosomal abnormality. None of the p53-deleted patients displayed additional low-risk aberrations, like t(8;21) or inv(16). Significant positive association between p53 deletion and other high-risk factors was identified for del(5q) (P<0.001), -5 (P<0.001) and -7 (P<0.05). The molecular risk factors FLT3-ITD and NPM1 mutation showed an inverse correlation to the p53 deletion in complex aberrant patients (P<0.001). The multivariate analysis revealed p53 deletion without multiple aberrations as an independent negative prognostic factor for disease-free survival (P<0.001), relapse risk (P=0.028) and overall survival (P<0.001). Thus, the single p53 deletion should be considered as a high-risk aberration for future risk-adapted treatment strategies in AML.

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17. Ann Oncol. 2008 Nov;19(11):1882-7. doi: 10.1093/annonc/mdn403. Epub 2008 Jul 31.

Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie.

Al-Batran SE(1), Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, Stoehlmacher J, Clemens MR, Mahlberg R, Fritz M, Seipelt G, Sievert M, Pauligk C, Atmaca A, Jäger E.

Author information:
(1)Klinik für Onkologie und Hämatologie, Krankenhaus Nordwest, Frankfurt, Germany. albatran@aol.com

BACKGROUND: The combination of docetaxel (Taxotere), cisplatin, and fluorouracil improved efficacy in gastric cancer, but was associated with substantial toxicity. This study was designed to incorporate docetaxel into a tolerable biweekly (once every 2 weeks) oxaliplatin-based chemotherapy regimen.
PATIENTS AND METHODS: Patients with measurable, metastatic adenocarcinoma of the stomach or esophagogastric junction and no prior chemotherapy received oxaliplatin 85 mg/m(2), leucovorin 200 mg/m(2), and fluorouracil 2600 mg/m(2) as a 24-h infusion in combination with docetaxel 50 mg/m(2) (FLOT) on day 1 every 2 weeks. Prophylactic growth factors were not administered.
RESULTS: Fifty-nine patients were enrolled; 54 received treatment. Patients had a median age of 60 years (range 29-76) and most (93%) of them had metastatic disease. Objective responses were observed in 57.7% of patients with a median time to treatment response of 1.54 months. Median progression-free survival (PFS) and overall survival were 5.2 and 11.1 months, respectively. Twenty-five percent of patients experienced prolonged (>12 months) PFS. Frequent (>10%) grade 3 or 4 toxic effects included neutropenia in 26 (48.1%), leukopenia in 15 (27.8%), diarrhea in 8 (14.8%), and fatigue in 6 (11.1%) patients. Complicated neutropenia was observed in two (3.8%) patients, only.
CONCLUSIONS: Biweekly FLOT is active and has a favorable safety profile.

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PMID: 18669868 [PubMed - indexed for MEDLINE]

18. Ann Oncol. 2008 Feb;19(2):340-7. Epub 2007 Oct 24.

Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer.

Boeck S(1), Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, Boeck HP, Schmid B, Kettner E, Stauch M, Lordick F, Ko Y, Geissler M, Schoppmeyer K, Kojouharoff G, Golf A, Neugebauer S, Heinemann V.

Author information:
(1)Medizinische Klinik und Poliklinik III, Klinikum Grosshadern, Ludwig-Maximilians-Universität München, Germany.

BACKGROUND: To compare the efficacy and safety of three different chemotherapy doublets in the treatment of advanced pancreatic cancer (PC).
PATIENTS AND METHODS: At total of 190 patients were randomly assigned to receive capecitabine 1000 mg/m(2) twice daily on days 1-14 plus oxaliplatin 130 mg/m(2) on day 1 (CapOx), capecitabine 825 mg/m(2) twice daily on days 1-14 plus gemcitabine 1000 mg/m(2) on days 1 and 8 (CapGem) or gemcitabine 1000 mg/m(2) on days 1 and 8 plus oxaliplatin 130 mg/m(2) on day 8 (mGemOx). Treatment cycles were repeated every three weeks. The primary end point was progression-free survival (PFS) rate at 3 months; secondary end points included objective response rate, carbohydrate antigen 19-9 response, clinical benefit response, overall survival and toxicity.
RESULTS: The PFS rate after 3 months was 51% in the CapOx arm, 64% in the CapGem arm and 60% in the mGemOx arm. Median PFS was estimated with 4.2 months, 5.7 months and 3.9 months, respectively (P = 0.67). Corresponding median survival times were: 8.1 months (CapOx), 9.0 months (CapGem) and 6.9 months (mGemOx) (P = 0.56). Grade 3/4 hematological toxicities were more frequent in the two Gem-containing arms; grade 3/4 non-hematological toxicity rates did not exceed 15% in any arm.

CONCLUSION: CapOx, CapGem and mGemOx have similar clinical efficacy in advanced PC. Each regimen has a distinct but manageable tolerability profile.

DOI: 10.1093/annonc/mdm467
PMID: 17962204 [PubMed - indexed for MEDLINE]

19. Crit Rev Oncol Hematol. 2007 Oct;64(1):64-72. Epub 2007 Feb 20.

Pegfilgrastim supports delivery of FEC-100 chemotherapy in elderly patients with high risk breast cancer: a randomized phase 2 trial.

Romieu G(1), Clemens M, Mahlberg R, Fargeot P, Constenla M, Schütte M, Easton V, Skacel T, Bacon P, Brugger W.

Author information:
(1)CRLC Val d'Aurelle, Montpellier, France.

This randomized phase 2 study explored the feasibility of delivering four to six cycles of the dose-intensified regimen FEC-100 (5-fluorouracil, epirubicin, and cyclophosphamide) to elderly patients with stage II-III breast cancer, using pegfilgrastim for neutrophil support. Sixty patients aged 65-77 years received single 6mg doses of pegfilgrastim on day 2 of FEC-100, either as primary prophylaxis (all cycles: PP), or as secondary prophylaxis (all cycles following a neutropenic event: SP). Neutropenic events (a composite endpoint that included grade 3 neutropenia+fever, grade 4 neutropenia, infectious complication requiring systemic anti-infectives and chemotherapy dose delay/reduction) occurred in 24/30 (80%) of the PP and 21/29 (72%) of the SP group in the first cycle. Most patients received all chemotherapy cycles at full dose on schedule (26/30 [87%] PP; 20/29 [69%] SP). These data indicate that delivery of FEC-100 is feasible with pegfilgrastim support in elderly breast cancer patients.

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PMID: 17317205 [PubMed - indexed for MEDLINE]

20. Leukemia. 2006 Apr;20(4):707-14.

Reduced intensity conditioning allows for up-front allogeneic hematopoietic stem cell transplantation after cytoreductive induction therapy in newly-diagnosed high-risk acute myeloid leukemia.

Platzbecker U(1), Thiede C, Füssel M, Geissler G, Illmer T, Mohr B, Hänel M, Mahlberg R, Krümpelmann U, Weissinger F, Schaich M, Theuser C, Ehninger G, Bornhäuser M.

Author information:
(1)Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus, Dresden, Germany. Uwe.Platzbecker@uniklinikum-dresden.de

There is substantial need to improve the outcome of patients with high-risk acute myeloid leukemia (AML). The clinical trial reported here investigated a new approach of up-front allogeneic hematopoietic stem cell transplantation (HSCT), provided a median of 40 days (range 22-74) after diagnosis, in twenty-six consecutive patients with newly-diagnosed high-risk AML characterized by poor-risk cytogenetics (n = 19) or inadequate blast clearance by induction chemotherapy (IC, n = 7). The median age was 49 years (range 17-68). During IC-induced aplasia after the 1st (n = 11) or 2nd (n = 15) cycle, patients received allogeneic peripheral blood stem cells (PBSC) from related (n = 11) or unrelated (n = 15) donors following a fludarabine-based reduced-intensity regimen. Seventeen patients were not in remission before HSCT with a median

marrow blast count of 34% (range 6-70). All patients achieved rapid engraftment and went into remission with complete myeloid and lymphatic chimerism. Grades II to IV acute GvHD occurred in 14 (56%) and extensive chronic GvHD was documented in 8 (35%) patients. The probability of disease-free survival was 61% with only three patients relapsing 5, 6 and 7 months after transplantation, respectively. Up-front allogeneic HSCT as part of primary induction therapy seems to be an effective strategy in high-risk AML patients and warrants further investigation.

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Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL).

Wassmann B(1), Pfeifer H, Stadler M, Bornhaüser M, Bug G, Scheuring UJ, Brück P, Stelljes M, Schwerdtfeger R, Basara N, Perz J, Bunjes D, Ledderose G, Mahlberg R, Binckebanck A, Gschaidmeier H, Hoelzer D, Ottmann OG.

Author information:
(1)Departments of Hematology/Oncology of University Hospitals Frankfurt, Hannover, Dresden, Münster, Ulm, Heidelberg, Munich, Germany.

In adult Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), minimal residual disease (MRD) after stem cell transplantation (SCT) is associated with a relapse probability exceeding 90%. Starting imatinib in the setting of MRD may decrease this high relapse rate. In this prospective multicenter study, 27 Ph+ ALL patients received imatinib upon detection of MRD after SCT. Bcr-abl transcripts became undetectable in 14 (52%) of 27 patients, after a median of 1.5 months (0.9-3.7 months) ((early)CR(mol)). All patients who achieved an (early)CR(mol) remained in remission for the duration of imatinib treatment; 3 patients relapsed after imatinib was discontinued. Failure to achieve polymerase chain reaction (PCR) negativity shortly after starting imatinib predicted relapse, which occurred in 12 (92%) of 13 patients after a median of 3 months. Disease-free survival (DFS) in (early)CR(mol) patients is 91% +/- 9% and 54% +/- 21% after 12 and 24 months, respectively, compared with 8% +/- 7% after 12 months in patients remaining MRD+ ($P < .001$). In conclusion, approximately half of patients with Ph+ ALL receiving imatinib for MRD positivity after SCT experience prolonged DFS, which can be anticipated by the rapid achievement of a molecular complete remission (CR). Continued detection of bcr-abl transcripts after 2 to 3 months on imatinib identifies patients who will ultimately experience relapse and in whom additional or alternative antileukemic treatment should be initiated.

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Antimicrobial therapy of unexplained fever in neutropenic patients--guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society).

Link H(1), Böhme A, Cornely OA, Höffken K, Kellner O, Kern WV, Mahlberg R, Maschmeyer G, Nowrousian MR, Ostermann H, Ruhnke M, Sezer O, Schiel X, Wilhelm M, Auner HW; Diseases Working Party (AGIHO) of the German Society of Hematology and

Oncology (DGHO); Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society).

Author information:
(1)Dept. of Internal Medicine I, Medizinische Klinik I, Westpfalz-Klinikum, Hellmut-Hartert-Strasse 1, 67655, Kaiserslautern, Germany. hlink@rhrk.uni-kl.de

Cytostatic chemotherapy of hematological malignancies is often complicated by neutropenia, which increases the risk of infections, especially if the neutrophil count is below 500/microl. Frequently, fever is the first, and in most patients the only, sign of an infection. Unexplained fever is defined as follows: temperature of >/=38.3 degrees C or >/=38.0 degrees C for at least 1 h, or measured twice within 12 h, if the neutrophil count is <500/microl or <1000/microl with predicted decline to 500/microl. Different risk categories can be identified according to the duration of neutropenia: low risk </=5 days, intermediate risk 6-9 days, high risk >/=10 days. An empirical mono- or duotherapy with antipseudomonal and antistreptococcal agents should be initiated immediately. In the low risk patient group, oral therapy with cipro-, levo-, or ofloxacin combined with amoxicillin/clavulanic acid is permissible. For standard and high risk patients, monotherapy can be carried out with either ceftazidime, cefepime, piperacillin with tazobactam or a carbapenem. In duotherapy, a single dose of an aminoglycoside is combined with acylaminopenicillin or a cephalosporin of the third or fourth generation. The addition of glycopeptides in empirical therapy should only be considered in the presence of severe mucositis, or if a catheter-associated infection is suspected. If fever persists after 72-96 h of first-line therapy with antibiotics, the regimen should be modified (with the exception of e.g. coagulase-negative staphylococci infections, because these infections take longer to respond). Intermediate risk patients should additionally receive an aminoglycoside after monotherapy (penicillin or a cephalosporin). If a carbapenem was administered for monotherapy, this can be followed by a quinolone and/or a glycopeptide. In the high risk group, the same modifications should be made as in the intermediate risk group but with additional systemic antifungal treatment. In the presence of unexplained fever, fluconazole can be administered at first, but if this fails, amphotericin B (conventional or liposomal), itraconazole, voriconazole or caspofungin should be started. After defervescence to <38 degrees C, treatment should be continued for 7 days if the neutrophil count is <1000/microl, and for 2 days if the neutrophil count is >1000/microl.

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The valency state of absorbed iron appearing in the portal blood and ceruloplasmin substitution.

Wollenberg P(1), Mahlberg R, Rummel W.

Author information:
(1)Institut für Pharmakologie und Toxikologie, Universität des Saarlandes, Homburg/Saar, Federal Republic of Germany.

(1) Attempts to determine the redox-state of the absorbed iron, which appeared in the portal blood when the free iron-binding capacity was previously saturated, indicate that about 30-90% of this iron was in the ferrous state. This effect was particularly prominent after luminal administration of ferrous iron, but was also seen when iron was given in the ferric state. (2) Total iron absorption is significantly higher in ceruloplasmin-substituted copper-deficient animals as

compared to copper-deficient controls. (3) The appearance rate of absorbed iron in the portal blood of copper-deficient animals increased several times immediately after the intravenous infusion of ceruloplasmin. (5) The distribution of absorbed iron was changed due to the ceruloplasmin substitution: it was increased in the reticulocytes (+66%), plasma (+400%) and the body (+112%), whereas in the liver it was decreased by about 78%. (5) In iron-deficient rats intravenously injected ceruloplasmin did not increase iron absorption. (6) The conclusion was drawn that, as for the entrance into the mucosa from the luminal side, also for the release at the contraluminal side into the portal blood, the ferrous state of iron is favoured and that ceruloplasmin accelerates the release into the portal blood by catalyzing the oxidation of ferrous iron due to its high Fe(II): oxygen oxidoreductase (EC 1.16.3.1) activity.

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